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64TH MEETING

ISSUE:

GUIDANCE DOCUMENTS ON DEVELOPING ANTIMICROBIAL DRUGS

GENERAL CONSIDERATIONS AND INDIVIDUAL INDICATIONS

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Grand Ballroom
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P R O C E E D I N G S

Opening Remarks

DR. CRAIG: Good morning. Welcome to the second day of the Anti-Infective Drug Advisory Committee meeting where we are talking about guidance documents on developing antimicrobial drugs.

One of the things that you will notice, or may have noticed, is that the members up here on the front table have a book that has copies of the FDA slides. I have been told by the FDA that they will be putting these on the Internet so that all of you will be able to eventually get them.

It will probably take a couple of weeks but that information will be available to you on the Internet.

Again, to start off this morning, we should go around the head table so that we can get all the names into the record.

DR. MURPHY: Dianne Murphy, Office Director, ODE4.

DR. CHIKAMI: Gary Chikami, Director, Division of Anti-infective Drug Products.

DR. ALBRECHT: Renata Albrecht, Deputy Director, Division of Special Pathogens and Immunologic Drug Products.

DR. MURRAY: Barbara Murray, University of Texas

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Medical School, Houston.

DR. RELLER: Barth Reller, Duke University Medical Center.

MS. McGOODWIN: Ermona McGoodwin, FDA.

DR. CRAIG: Bill Craig, University of Wisconsin.

DR. NORDEN: Carl Norden, University of New Jersey Medical Center.

DR. CHRISTIE: I am Celia Christie, University of Cincinnati College of Medicine, Children's Hospital Medical Center, Cincinnati, presently on sabbatical leave to Johns Hopkins.

DR. HENRY: Nancy Henry, Mayo Clinic.

DR. RODVOLD: Keith Rodvold, University of Illinois at Chicago.

DR. SOPER: David Soper, Medical University of South Carolina at Charleston.

DR. CHESNEY: Joan Chesney, University of Tennessee in Memphis.

DR. WITTES: Janet Wittes, Statistics Collaborative.

DR. CRAIG: Thank you.

We have a very heavy schedule today, a lot more topics to discuss. So I am encouraging all the speakers to

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sort of be concise and keep within the time so that we will still have adequate time for discussion.

We will gain about a half an hour since there will be no open public hearing but I don't want people, again, to use that as an excuse for taking a longer period of time.

We are going to change the schedule a little bit this morning. We are going to start off first with complicated urinary-tract infections and pyelonephritis and then go to the general clinical considerations.

The FDA presentation on complicated urinary-tract infections and pyelonephritis will be by Regina Alivisatos.

Complicated Urinary-Tract Infections and Pyelonephritis

FDA Presentation

DR. ALIVISATOS: Good morning.

[Slide.]

In the next fifteen minutes, I would like to go through the indication of complicated urinary-tract infections and acute pyelonephritis.

[Slide.]

In the 1992 points to consider document, which has now been incorporated into the current guidance document, the infections of the urinary tract are divided into the uncomplicated urinary-tract infections and the complicated

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urinary-tract infections including pyelonephritis.

Additionally, one statistically adequate, well-controlled trial establishing equivalence or superiority versus an approved comparator and one open, uncontrolled trial establishing equivalence to the success rate of the comparator are suggested in order to obtain approval for this indication.

[Slide.]

The pyelonephritis indication is also referred to in the original 1992 document. Specifically, pyelonephritis is studied with complicated urinary-tract infections. Thirty evaluable patients are suggested per arm. The primary efficacy variable is microbiological. An evaluable patient should be clinically and microbiologically evaluable and good correlation should exist between clinical cure and bacteriologic outcome.

[Slide.]

To go back a little bit, the advisory committee, in March of 1997, dealt with the issue of uncomplicated urinary-tract infections. The main conclusion from that meeting was not to accept as evaluable patients with colony counts of less than 10^5 colony-forming units per milliliter.

This is, as opposed to the IDSA FDA 1992

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guidelines that do accept as evaluable patients with colony counts of less than 10^5.

[Slide.]

As pertains to the indication that we are discussing this morning, there are differences between the IDSA FDA 1992 guidelines and the current guidance document, specifically the IDSA FDA guidelines suggest studying pyelonephritis separately whereas the FDA studies them together.

The division's position is that the type and duration of therapy for these entities are the same and, therefore, they can be studied together in order to facilitate drug development.

Additionally, the IDSA FDA guidelines suggest as accepting as evaluable patients with pyelonephritis with colony counts of greater than or equal to 10^4 colony-form units per milliliter whereas the FDA continues to suggest as accepting as evaluable patients with greater than or equal to 10^5.

[Slide.]

As to the definition of complicated urinary-tract infections, a clinical syndrome that may appear in men or women accompanied by the systemic signs and symptoms of

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fever, chills, malaise, the local signs and symptoms, flank pain, back pain, costovertebral-angle pain or tenderness in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization.

[Slide.]

The predisposing conditions that constitute functional or anatomical abnormalities of the urinary tract include the presence of an indwelling catheter, 100Êmilliliters of residual urine after voiding or neurogenic bladder, obstructive uropathies such as nephrolithiasis or fibrosis, azotemia due to intrinsic renal disease, urinary retention in men possibly due to benign prostatic hypertrophy.

[Slide.]

Pyelonephritis is a systemic ascending urinary-tract infection often accompanied by bacteremia, the same pathogen in the blood and the urine. Again, it is characterized by the presence of the systemic and local signs and symptoms of an ongoing infectious process, again, malaise, chills, fever, back pain, flank pain, et cetera.

However, a predisposing anatomical or functional abnormality of the urinary tract is not present. I would like to point out that the signs and symptoms of

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pyelonephritis are the same as those seen in complicated urinary-tract infections in general.

The FDA does recognize that there are complicated and uncomplicated pyelonephritides. However, once again, the type and duration of therapy for these entities are the same and, therefore, we continue to suggest that they be studied together.

[Slide.]

The duration of therapy, or the duration of systemic exposure to the antimicrobial is usually a minimum of seven days to a maximum of fourteen days depending on the drug regimen.

[Slide.]

Consideration should be given during therapy to transition from an intravenous route of administration to an oral route. This would be dependent upon a determination of clinical response at predetermined time points.

[Slide.]

Included are patients who, in the presence of a functional or anatomical abnormality of the urinary tract, develop the signs and symptoms of the disease--fever, chills, flank pain, et cetera--the above should be accompanied by a positive pre-treatment urine culture which

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should be obtained within 48 hours of enrollment and is defined as the presence of a uropathogen in an amount greater than or equal to 10^5 colony-forming units per ml of an accepted uropathogen.

In vitro susceptibility testing of the uropathogen to the test and control drug should also be performed.

[Slide.]

The urine culture specimen should be obtained by sterile technique. Foley catheter bag specimens are not acceptable and, in chronically catheterized patients, if there is more than one isolate in the urine, all isolates should be considered contaminants unless the same pathogen or pathogens are isolated from simultaneously obtained blood cultures.

[Slide.]

Excluded are patients who have prostatitis, intractable infection that requires greater than 14 days of therapy such as an abscess, treatment with another antimicrobial within 48 hours, or within 24 hours if only a single dose, and in the absence of an appropriate positive culture and [atients who have uncomplicated urinary-tract infections, renal transplantation, ileal loops or vesico-ureteral reflex.

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[Slide.]

The evaluation visits can be divided into three groups. The baseline visit which should take place between study days -2 to 0, the first day of the study, or within 48Êhours prior to starting therapy. This visit should include an assessment of the patient's history, physical exam, vital signs, a pregnancy test when appropriate, a quantitative urine culture and sensitivities.

Compatibility with the inclusion and exclusion criteria should be assessed. Informed consent should be obtained. Randomized is allowed prior to the availability of the culture report.

The on-therapy visit is optional and should take place between study days 3 to 7. This visit may coincide with transition from an IV mode of administration to an oral mode. An assessment of clinical efficacy, therefore, is performed.

The first post-therapy visit is the FDA test-of-cure visit and should take place five-to-nine days after the completion of therapy. At this visit, an assessment of clinical and microbiological efficacy--in other words, a urine culture--should be obtained.

The final visit, which may coincide with the end

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of the study, should take place four-to-six weeks after the completion of therapy. The purpose of this visit is to assess for relapse or recurrence and, again, an assessment of clinical and microbiological efficacy should be performed.

[Slide.]

A patient is considered evaluable with a valid five-to-nine-day post-therapy visit. The purpose of the four-to-six-week post-therapy visit is to assess for recurrence or new infection.

[Slide.]

Microbiological outcome is assessed in clinically evaluable patients with a baseline pathogen in an amount of greater than or equal to 10^5 colony-forming units per milliliter. At the five-to-nine-day post-therapy visit, we can have the following outcomes: eradication, a urine culture obtained within the five-to-nine-day window that reveals that the uropathogen isolated an entry in an amount of greater than or equal to 10^5 has been reduced to less than 10^4 colony-forming units per milliliter; persistence, a culture obtained at the five-to-nine-day visit that grows greater than or equal to 10^4 colony-forming units of the original pathogen, and this would subsequently be carried

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forward as a failure.

[Slide.]

Superinfection, a urine culture from which greater than or equal to 10^5 colony-forming units per milliliter of a uropathogen other than the baseline pathogen is isolated during the course of active therapy and is associated with signs and symptoms of active infection. These patients, again, would be carried forward as failures.

A new infection, the isolation of a uropathogen other than the original uropathogen, again, in an amount of greater than or equal to 10^5 colony-forming units per milliliter any time after therapy is completed.

[Slide.]

At the four-to-six-week post-therapy visit, microbiologic outcomes include sustained eradication, again a culture obtained with the four-to-six-week window, that reveals that all uropathogens obtained at entry in an amount greater than or equal to 10^5 remain reduced to less than 10^4 colony-forming units per milliliter.

Persistence; these are basically the failures carried forward. Superinfection as defined before, greater than or equal to 10^5 with signs of infection, and this culture would be obtained during therapy.

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[Slide.]

Recurrence, the isolation of the original uropathogen in the amount of greater than or equal to 10^5 colony-forming units per milliliter any time after the documented eradication of this organism at the five-to-nine-day post-therapy or test-of-cure visit. And new infection, the isolation of a pathogen other than the original pathogen in an amount of greater than or equal to 10^5 anytime after therapy was completed.

[Slide.]

Clinical outcome is assessed in clinically evaluable patients; in other words, those patients who met the definition of the disease, the inclusion-exclusion criteria, have complied with the regimen and who returned for the visit.

At the five-to-nine-day post-therapy visit, the outcomes include cure, the complete or significant resolution of all signs and symptoms, failure, no response to therapy or worsening of most or all pre-therapy signs and symptoms. The category of improvement has been omitted in order to provide for a dichotomous cure-fail analysis.

[Slide.]

At the four-to-six-week post-therapy visit,

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outcomes include sustained cure, all pre-therapy signs and symptoms remain resolved at the four-to-six-week post-therapy visit. Failure; all patients who were failures previously are carried forward and relapse, the signs and symptoms absent at the five-to-nine-day post-therapy visit that reappear at the four-to-six-week post-therapy visit.

[Slide.]

Just to mention, any patient who receives an antimicrobial for an non-urinary-tract indication capable of eradicating a uropathogen during therapy or during the full study period should be considered unevaluable.

[Slide.]

Usually, complicated urinary-tract infections and pyelonephritides are caused by organisms from the family of the Enterobacteriaceae. Additionally, Enterococci and Pseudomonas species are also found.

[Slide.]

Routinely, coagulase-negative Staphylococci and non-Group-D Streptococci are considered contaminants and they are not considered pathogens. Additionally, and as I said before, multiple organisms--in other words greater, actually, than one organism in a urine culture--those organisms should be considered contaminants unless the

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organism or organisms are isolated from simultaneously obtained blood cultures.

That concludes my presentation. I would like to ask for questions and then comments or recommendations from the committee.

DR. CRAIG: Any questions or clarifications?

If not, the comments from the committee will come from Barth Reller.

Committee Presentation

DR. RELLER: First, I would like to congratulate Dr. Alivisatos and colleagues on capturing so well the consensus that was reached in the revision of this proposed guideline from the discussion that took place in March of '97 that begins on page 34 in the back of our blue books.

It is enlightening, in reading some comments going back, for example, Dr. Marian Melish's superb discussion of the issues that we readdressed yesterday with acute otitis media, reading some of the other of our comments, like myself, it is sobering to see it in print.

But, out of that discussion and the summation that we have just heard, there are three points that I would like to comment on. The first one is the selection or the maintenance, despite a difference from the IDSA guidelines,

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of the 10^5 criteria for entry. In the discussion that took place in the agency, and all of us have found Dr. Calvin Kunin's book on Urinary-Tract Infections, Diagnosis, Prevention and Management, the Fifth Edition in 1997, to be extremely useful.

I don't think it can be said more succinctly than he did in a bullet for the reasons, the discussion about bacteriologic criteria for urinary-tract infection. And I quote, "Strict criteria equal to or greater than 10^5 CFU per ml of uropathogens are required for clinical trials to avoid overdiagnosis and allow an endpoint for cure."

The committee felt, after much discussion, that, indeed, that is the case. There is a small loss, a very small loss, in sensitivity for complicated infections, a larger loss of uncomplicated but, nonetheless, a worthwhile price to pay for the specificity derived from clinical trials.

Moreover, it makes the assessment, after therapy, much more objective, reproducible, to have the diagnostic establishing infection at 10^5 or greater, and then it allows the 10^4 or less than 10^4, specifically, and, importantly, less than 10^4, with those who maintain colony counts of 10^4 or greater as being persisters and then, eventually,

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categorized at late follow up, finally, as those who have superinfections, new infections, or relapsing infection.

The second issue that I would like to comment on is, in this category of infections of complicated, and I concur totally with the fusion of these entities into two broad categories, the uncomplicated and the complicated that we are discussing today with the caveat that Dr. Craig mentioned and we have been assured will take place of inclusion of men in the complicated urinary-tract-infection category in clinical trials.

That is that patients with complicated infection owing to stones, indwelling catheters of patients who then become septic who frequently, when they truly have acute pyelonephritis complicating an indwelling catheter, frequently have bacteremia, published figures on the order of 20, 30, 40, 50 percent.

Hence, the concept of, in part, an intent to really delineate those patients with the entity as opposed to finding those patients out of that vast sea of patients appropriately or most frequently or often inappropriately who are patients who become febrile for whatever reason lying debilitated, often in an extended-care facility or a chronic-care unit in the hospital with an indwelling

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catheter where there are multiple organisms in the urine and what do you make of two, three, four organisms all of which are over 10^4, 10^5 and often even higher counts.

Hence, the attempt, if it is not a sole uropathogen, more than 100,000 organisms to restrict those patients who would be included in the trials to those with multiple organisms if one of those organisms which would occur 20 to 50 percent of the time in the complicated infections also appeared in the blood.

So I think that is a reasonable way of trying to steer between the one rock and the whirlpool of trying to get those that really have the problem.

I would suggest a slight refining in the final wording. I would not call those multiple organisms in the catheterized patients contaminants but rather something along the lines of a polymicrobial colonization because I think "contaminants" has an offensive tone to it in the sense that you did something wrong.

Now, it may be wrong if you collect it from the bag but if one aspirates the appropriate port, indeed, as Kunin has pointed out, these patients do have polymicrobial colonization. They have a polymicrobial infection of the urine most of the time which is asymptomatic and definitely

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should not be treated unless they become septic and it is empiric treatment and then one is often stuck with what grows out of the blood or that on-therapy culture with the multiple organisms.

But for the purposes of clinical trial, at the end of the day trying to assess response of a specific pathogen to therapy, I think one would find it extraordinarily difficult as a reviewing officer or an analyzer of the clinical trial to make sense out of a urine culture in a febrile patient with a catheter without a positive blood culture who had four different organisms in the urine.

So it is a practical issue of inclusion of patients reaching for specificity again with that concept and what is important for a clinical trial in assessing efficacy in a category of infection that we know is going to have an efficacy rate much lower than the uncomplicated infections.

The last thing that I would like to suggest is again a refinement of the definitions in the final version for consistency. On pages 7 and 8 in our blue book at tabÊI, I think the definitions in the colony counts are spot-on for these different entities but I would call the persisting infections and the ones that are still there at

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six weeks reinfection as the broad category and then have them separated into--excuse me; the broad term should be recurrence.

Then the recurrences are separated into reinfection or one could call it new infection that should not penalize the sponsor or the firm having to do with success initially and those that are relapses. They may have been there at early follow up at 10^4 or more and, at late follow up, maybe they are 10^4 or more or 10^5 or 10^6 and it is the same organism.

Now, there is the presumption that it is the same organism, that it is the same genus and species. In the clinical trials, since it is so easy nowadays to do and so inexpensive and so readily available, in the clinical trials, I would strongly encourage the agency to have sponsors and encourage the sponsors to look at these organisms that are of the same genus and species and fall into the recurrence category and a presumptive relapse of the same organism.

They should be encouraged to do, for example, like pulse-field gel eletrophoresis on the early and the later organism because, again, if it is the same organism, it denotes something quite different for the patient and it

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also is truly a failure of the drug to eradicate the organism in these complicated infections as opposed to if it be a different organism, it would be in the same category as reinfection and would not be a failure of antimicrobial therapy for a complicated urinary-tract infection.

So the numbers are right. The wording could be refined to make those distinctions that I think are well recognized in the literature and have therapeutic implications for the investigation patient and have important implications in terms of properly assessing the efficacy of the studied compound for the therapy of these infections.

We discussed this at great length the last time. I am very pleased with what has been done with that discussion in putting it succinctly into the revised document would only suggest the revisions or refinements mentioned.

Committee Discussion

DR. CRAIG: Comments?

DR. SOPER: Did I understand you correctly in that you are going to lump complicated urinary-tract infections with uncomplicated pyelonephritis and study them as a single entity?

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DR. RELLER: The intent was to separate uncomplicated infections from complicated ones. If an investigation had acute pyelonephritis, for example, an appreciable number of whom will also have positive blood cultures and denotes an upper-tract focus, yes, that would be included in the complicated infections.

DR. ALIVISATOS: That's correct.

DR. SOPER: I think that your explanation for that was that the duration of therapy was similar, but I am not sure that they are the same patient. The off-the-street, de novo, acute pyelonephritis is not the same as a patient that has an indwelling catheter, a stone or something else that is going to require some sort of intervention.

It would be my recommendation that those patients be studied separately.

I have one other comment, too. My other comment is I have a problem with using the word "eradication" when it is not really eradication. You are saying that you have eradicated the uropathogen if the colony count is less than 10^4. That ain't gone. That ain't zero. So it sends the wrong message.

You really haven't eradicated the microorganism unless it is sterile.

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DR. ALIVISATOS: That's true. It is semantics. We will defer to the micro people in a moment for that. For an uncomplicated pyelonephritis, it is certainly true that if you have a patient that has a stone in place, for example, as opposed to that, that the duration of therapy might be longer. There is a range, usually, of therapy.

Usually, as I said before, seven-to-fourteen days, although it is ten to fourteen days often in clinical practice, whether it is IV or oral. But this is a clinical trial. A patient who goes more than fourteen days might be considered a failure. It is for purposes of studying. It is not clinical practice, how we would treat a patient, necessarily.

I don't know. Maybe Dr. Albrecht or Dr. Goldberger have some comment on this.

DR. SOPER: I guess I am just saying that, to me, it is a bit of apple/orange issue that if I read a study on pyelonephritis and all of the patients have indwelling catheters, that is not the same as a study that I might read that are all women without catheters or other predisposing factors.

You have kind of lumped the uncomplicated pyelonephritis in with the complicated UTIs here, and I

guess I just have a problem with that.

DR. MURRAY: Does that include perinephric abbesses associated with UTIs? Do those go in this group, too?

DR. ALIVISATOS: A patient with a perinephric abscess often will require greater than fourteen days of therapy so they would be excluded based on the exclusion criteria where we say that somebody who might require greater than fourteen days might be excluded.

When I spoke--it is not in the document--an example of that would be an abscess. So, no; they wouldn't be. Again, as to the pyelonephritis issue, I think that when we are speaking of pyelonephritis, and what we see when we look at trials, are usually women who do not have indwelling catheters. So I agree with you on some level but, on some level, what we are seeing and what we are talking about is different and possibly we could refine the document to express that.

As to the microbiology issue, maybe Dr. Altaie--what we mean by eradication, and I agree eradicated means eradicated; it is not there. This is a microbiological definition that was used.

DR. ALTAIE: To try to address the eradication,

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the techniques of culturing these urines are allowing for sloppiness which is a sneeze on a plate, a finger on a plate, or things growing out of the media, itself, that you cannot distinguish after incubation.

So, traditionally, I like to see--or a microbiologist likes to see--around ten colonies before they call them a real thing on the plate. So 10^4, actually, translates to ten colonies on the plate. When you go below that, you are looking at eight, nine, whatever--just to have an assurance of what you see is real and coming from the patient.

I agree that it is not eradication. I agree we would like to see less than that. But if you started with 100 colonies and ended up with less than ten, I say the drug is doing something and it is on the way to clear up. And then we have the follow up. So that is the little logistics behind the less than 10^4 colonies.

DR. SOPER: I don't disagree with that. I just disagree with the way you have--

DR. ALTAIE: The term.

DR. SOPER: Yes.

DR. ALBRECHT: Let me just make a comment about the complicated UTI versus pyelonephritis. I think we do

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recognize that, as is stated in the document, the intent of combining the study of those types of patients was really a practical consideration.

We thought because the dosing and duration are similar that it might be convenient to enroll patients in those studies. There is also the issue of having adequate numbers to overall assess safety and efficacy.

As stated in the document, however, we do look at patients with complicated UTI separately from patients with acute pyelonephritis and, in fact, would expect to have adequate numbers of both types of populations before we would recommend approving the drug for such a use.

DR. SOPER: Is there a reason why you didn't require two randomized clinical trials for these agents when you suggest that there should be two randomized clinical trials for other agents, for other diseases?

Don't you say one statistically adequate RCT and the other one could be an uncontrolled--

DR. ALBRECHT: Do you mean in the context of complicated UTI and pyelo?

DR. SOPER: Yes; the points to consider is--we have one randomized controlled trial and then one uncontrolled observational trial; right?

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DR. ALBRECHT: It is not comparative but it actually does use the same criteria as the complicated. Again, I would say this is a practical consideration and really answer it in contrasting it to uncomplicated UTI. There are a lot of patients available for uncomplicated urinary tract so we assume we will get adequate, large studies where we can assess the efficacy of the agent.

However, in complicated UTI and pyelo, we assume that there are fewer patients. This is something that we have surmised based on NDAs submitted in the past and, therefore, the belief was that if we asked for one randomized, clinical trial--that is, an adequate and well-controlled study--we determine what the efficacy is compared to a proven control, that, then, if we use that information and a noncomparative study showing what the role of the drug is, that we can take the two pieces of information in context to recommend approval.

Again, it was sort of a practical consideration of there may not be enough patients and it may not be feasible to request both and how can we maximize the information we can get from the patients that will be studied?

DR. CHIKAMI: Just a quick comment to follow up on that. I think when the original points-to-consider

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documents were developed, the other consideration was that anti-infective products are often developed for multiple indications so a product that might be developed, or being studies for complicated urinary-tract infections would also be studied for uncomplicated urinary-tract infections, understanding that there are pathophysiologic differences.

But in the context of an entire drug-development program, we might be able to get corroborative data for safety and efficacy from some of these other indications in related sites of infection.

So, in looking at the overall package, the recommendations were developed to try and see where we can get the pieces to the puzzle that would all fit to support safety and effectiveness.

DR. MURRAY: Would the randomization or the analysis between the comparator and the study drug include whether they were truly acute uncomplicated pyelo or stone or catheter-associated because you might expect different cure rates or at least different relapse rates.

So will that be taken into account?

DR. ALIVISATOS: You usually do see analyses for each population, so you will see a separate analysis for patients with pyelo, a separate analysis for patients who

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are chronically catheterized, et cetera. It doesn't necessarily mean when something is approved that each group was successfully cured, except for pyelo.

DR. CRAIG: But I have seen in the past where someone decided to study the drug in the worst scenario looking primarily in males where they beat the comparator by a long shot. But, because it wasn't the very high percentages that you see in acute pyelonephritis, they were forced to do another study.

So I think, clearly, there are different response rates when you look at the different groups and that needs to be taken into consideration when one is looking at comparing results.

DR. NORDEN: I have a couple of comments. Many of them are along the same line that Dr. Soper raised. I don't want to completely rehash what other people have said but I think it is very important that you analyze the two groups separately.

The presence of obstruction or the presence of stone is the major factor that mitigates against success and certainly mitigates in favor of recurrence. People with acute uncomplicated pyelo, yes, they are upper urinary-tract infection but they are certainly not the same.

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That is number one. The second is, forgetting the semantics of eradication, I think, to me, at least clinically, there is an implication that if a patient has 10^4 of the same organism that they had when they started, the likelihood that they are going to do worse, recur, whatever, when the antibiotics have been withdrawn is much greater than if the patient has zero colonies, even with a one-one-thousandth of an ML loop plated out.

So I know I read everything in the blue book before the discussion about what we should accept. I have trouble with accepting, I guess, 10^4 as a point of success. It may be success. It may be partial success, but I am not convinced.

DR. CRAIG: It is less than 10^4.

DR. NORDEN: Less than 10^4 but it still could be between 10^3 and 10^4. Then the final comment is just the switch to oral therapy which is clearly going to occur. Nobody is going to be kept in the hospital for fourteen days of IV or ten days. I think that is fine. But we should have a predefined time frame in which you switch to oral because I think that you don't want to do it based on how the patient is doing.

You can do perfectly well with oral drugs. You

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get wonderful levels in the urine. That is not an issue. If we are going to say that oral drugs are acceptable, they should just be given at a fixed time frame rather than--the statement in here is that dependent on a determination of clinical response at predetermined time points.

If the patient isn't doing well with IV, they are probably not going to do well with more IV. I am just saying that somewhere in there you can say between four and seven days, it is acceptable to switch, or however you want to do it. But the switch shouldn't be dependent on the patient's clinical response.

I haven't made it clear. Everybody is looking skeptically.

DR. SOPER: I guess I would not like to see some predetermined parenteral duration because in patients that probably respond, you are going to want to switch them to oral almost immediately. As a matter of fact, you may even want to design a study in which you treat everybody with oral because with the antibiotics that are literally as good orally as they are systemically, you just are looking for--and, as Carl points out, it is the urinary concentration of the agent and they are excellent and there is no need to proscribe that.

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The issue is the pharmacokinetics of the agent regardless of how they are administered.

DR. CRAIG: I would disagree with what Dr. Reller wanted to do in terms of renaming things in terms of relapse. I think some of those concepts that Dr. Kunin initially put through don't necessarily hold up anymore. I think that, quite clearly, relapse in a male does usually reflect some focus in the urinary tract where the organism has been not eliminated.

But I think more and more of the studies in women are showing that really where the organism hasn't been eliminated is from the vaginal vestibule. So the pathogenesis of the infection is still a recurrence, is an ascending infection.

It is not that the organism is in the kidneys somewhere and has not been eliminated. So I think persistence is persistence and new infection with a new organism is a new infection. But breaking them down as to whether it is truly relapse, I think in women, most relapses actually would be considered reinfections from organisms that haven't been eliminated from the vaginal vestibule.

DR. MURRAY: The problem is they have used the definitions without the mechanism to distinguish between

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new--if the only way to tell it is new that it is not an E.coli, that is not very helpful. You could argue whether it is important to distinguish relapse versus new.

But that is the implication here and the methodology is not accounted for.

DR. CRAIG: All it says is it is different from the original microorganism. I think that leaves it up to what the companies want to do. If you are going to say that if that is the same species, whether using antibiograms to help show that it is a different organism or using serotyping and things like that, I think they say it is different from the original microorganism. They just haven't told you how to necessarily do it.

DR. ALTAIE: I need to add a little bit of comment to Dr. Murray's comments. She is right. We are basing these definitions only on genus and species. We all know genus and species can be different serotypes or different strains.

The only way to distinguish them is to do a molecular diagnostics there, pulse-gel electrophoresis or any other means. They are easy to do but we have traditionally faced resistance from the companies to do serotyping in these cases to distinguish them. So we are in

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a bind.

I agree, unless you have molecular diagnostics, you cannot precisely say these definitions are correct. They are based only genus and species at this time.

DR. SOPER: But even with those techniques, as Bill points out, in women, we may get the exact same microorganism that reinfects because it is unusual to see persistence in women.

DR. ALTAIE: That's true, also.

DR. NORDEN: I want to get a better sense from my colleagues on the committee, but is anybody else concerned about the less than 10^4 which allows as many as nine times 10^3, in theory, organisms if you use a one-one-thousandth loop.

To me, that is not necessarily the same--it is not the same response as zero organisms.

DR. CRAIG: If you look at the studies that have been done in males looking at bladder puncture versus voided urines, you can go way down on your cutoff point as far as showing that using 10^3, 10^2, without increasing your false positivity rate.

However, if you look at the studies in women and go down to 10^3, your false positivity rate of organisms that

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are just colonizing and not in the urinary tract goes up significantly high.

DR. NORDEN: And these are the same, Bill, as the organisms--

DR. CRAIG: These are people that have had bladder punctures as well as a voided urine to look at the numbers so that you have a significant false-positive rate when you go down to using numbers as low as 10^3. You increase your sensitivity. You pick up more because there are some patients that will only have lower colony counts.

But what you do is you increase your false positivity. So I think going up to--if you dropped it down to 10^3, you are going to call some failures that are not necessarily true failures and just maybe people that are colonized and will have a positive urine that way.

DR. NORDEN: But colonized with the same organism that they had at 10^5 before?

DR. CRAIG: Sure. They may not be entirely eliminated of the organism. That is very common with beta lactams that they frequently don't do that. That is why, oftentimes, in clinical trials, beta lactams don't look as well as what one finds as fluoroquinolones or T&P sulfa drugs that get into the vaginal secretions.

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DR. MURRAY: Plus, they are really not going to be able to tell if it is same organism or not.

DR. CRAIG: The only way they would be able to tell--

DR. MURRAY: Is by typing.

DR. CRAIG: Is by typing; right.

DR. MURRAY: I am not so worried about the fingers on the plate because that should be in a different place and shouldn't usually be an E.coli and that sort of thing. But the nonspecific contamination of the urine, itself, is a problem.

DR. SOPER: I guess I worry about that, too, Carl. But I assume that with complicated UTIs, that maybe the standard for cure needed to be softened a bit because it was unrealistic to expect, say, somebody with an indwelling catheter would actually get a sterile urine.

But I would have to predict that what you can do with antimicrobial therapy in those kinds of patients is that you can render them asymptomatic, eliminate the microorganism from their blood stream, decrease their colony counts to less than 10^3 and then watch as their colony counts, within a matter of days, grow back up to greater than 10^5 but not necessarily associated with ascending

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infection and its symptoms.

DR. CRAIG: The urine that we are looking at is five-to-nine days after therapy. So it is not the one immediately at the time the antibiotic has been stopped.

DR. SHELDON: Sheldon, FDA. I wanted to address the issue of a one-log reduction that you all are discussing. There is another way to interpret that information. If you produce a one-log reduction from 10^5 down to 10^4, in essence, you are effecting a biomass by reducing it by 90 percent. That is a significant impact on the biomass that you are dealing with.

For every log reduction thereafter, you increase it by 9 percent, by 0.9 percent, so you are having a significant impact when you produce a one-log reduction of the biomass, itself. It is just another way of interpreting the information and the efficacy of the drug at the site that you are studying.

DR. MURRAY: Maybe that is your term instead of eradication; reduction of biomass.

DR. CRAIG: I think if you look at the IDSA guidelines, the IDSA guidelines also sort of had gone down to a somewhat lower value for reduction. But it was less. It could be only a three-organism reduction, not a log.

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That is one of the reasons why we agreed to go with the higher number so that at least we were assured that we were getting at least over a log reduction in the number of bacteria.

DR. GOLDBERGER: Dr. Craig, we have several experienced FDA microbiologists over there. I just wonder if anyone could comment, as a practical matter, what has actually been seen in the trials or whether there is information from the clinical trials for some of the approvals as to whether or not we are talking about really 10^3 or whether most patients were, in fact, eradicated.

DR. ALTAIE: There is a very small number of patients that will end up with less than 10^4. If you add that 10^4 including as eradication, we gain nothing. So when a drug is working, the numbers clearly go to nothing.

That little bit of leeway relief does not include very many patients in a cure.

DR. CRAIG: But nothing based on, probably, 10^3 as the--

DR. ALTAIE: That's correct. The lower limit is 10^3. So you are looking for a clean plate. Most of the time, we do get clean plates. And those 10^4, even in a critical situation where it is approval versus non-approval

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for efficacy, they still cannot gain that if they include the 10^4. And we are saying less than 10^4.

So I think it is of limited use or worry for us to be looking at those patients really not being cured and being included as cures.

DR. GOLDBERGER: Are you saying, then, that as a practical matter, almost all patients are less then 10^3?

DR. ALTAIE: Yes; they usually are clean.

DR. RELLER: One other aspect of this discussion, and I bring it up, Carl, because I had argued strongly for less than 10^3 in the initial discussion. But, at the same, I recognize the important aspect of what one is trying to do in the follow-up cultures is to document persistence.

To have a fair objective marker of persistence early and categorization of the patient ultimately, one would need more than a single colony on the plate. Then, if you get a couple of colonies on the plate that are necessary to recognize at follow-up persistence and the reality is that, most of the time, these things are either clear or they are hovering up there and about to go over, as Dr. Soper said, if not at five-to-nine days, certainly at six weeks, they are way up there again.

Then we are talking about what is good enough to

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document persistence and yet is a fair biomass separator when we have kept the hurdle up high in the first place. I think the most important thing is to recognize that it is less than 10^4 that is the endpoint for successful therapy.

Bill, coming back to your point about the reworking of history on recurrence being divided into reinfection and relapse, I recognize, as Kunin pointed out in all of the wonderful pathophysiological work about that subset of patients who have recurring problems with infection in women and that, in fact, it may be the same organism that is causing anything from cystoureteritis to cystitis to recurrent more repetitive disease.

But I think it is still important to recognize that some of those lower-tract infections involve the upper track and they become an agonizing problem in terms of relapsing upper-tract infection rather than getting hung up on the importance of the distinction, most of the time that we may not have, although it is much easier to get now.

Fortunately, the incentives are in the right direction; that is, if you can show that it is a different organism, then you can have successful therapy even with organisms recurring. So there is every incentive to get the pulse-field-gel electrophoresis on the Enterobacteriaceae.

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But what I would recommend in the final document without having to get into a final conclusion on whether or not there is any validity to that distinction is at least let's not have different terms that, if not presently--and we could debate that--but historically clearly it implied different things that we not use the two terms with different implications but, rather, use one.

For example, under the clinical, we have sustained cure, failure and relapse. And then, microbiologically, we have persistent superinfection, recurrence and new infection. Why not call those that clinically come back again recurrences.

And then we have the recurrent--the same word is used for the ones that happen again and then realizing that you might further subdivide them if you have the means to do so.

Is there a reason for having recurrence clinically and relapse microbiologically?

DR. CRAIG: It is the other way around.

DR. RELLER: Right. There are two different terms.

DR. ALTAIE: Recurrence and relapse are clinical terms. New infection and reinfections are microbiological

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terms.

DR. MURRAY: You have got recurrence under microbiologic.

DR. ALTAIE: We internally have a debate on that and I defer that to Dr. Albrecht for historical reasons.

DR. ALBRECHT: I couldn't avoid this one. Let me mention that this is a historical issue, really, and it really is sort of a series of regulatory definitions that we have used fairly consistently in the last decade or two. After I talk, I guess I would invite my colleagues to make any further comments on this.

As Dr. Altaie pointed out, it is not always consistent with some of the microbiologic definitions that are used within the micro lab, but we have, as a regulatory agency, used the term "relapse" to refer to patients' clinical relapse. So, after improvement, if the patient gets worse, we refer to that as relapse and we are referring to the clinical signs and symptoms of the disease.

We have used the term recurrence to refer to the microbiological endpoint. So if a patient on therapy or end-of-therapy culture or post-therapy culture shows that the pathogen is not present and after that another culture is taken where the pathogen originally present is, again,

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isolated, we refer to that as recurrence.

If a new pathogen, not the one originally isolated at baseline, is isolated in this later culture, we refer to that as new infection. We have consciously stayed away from the term reinfection because we seem to have found different definitions. Sometimes, reinfection refers to the same pathogen, sometimes to the different pathogen.

Whether or not it is appropriate to distinguish new or same pathogen at the late evaluation is something that we can certainly debate, but that is simply the terminology that we have used in the past so that when an FDA reviewer says recurrence, they mean a pathogen is isolated again in the follow-up culture.

When they relapse, they mean the clinical signs and symptoms are there.

DR. MURRAY: But is inherently contradictory in a way because you are not doing methodology to tell you that it is the same pathogen. So you are persisting with the terminology that implies something that you have not shown. I have problems with that even if it is for historical purposes.

DR. CRAIG: Because a relapse could be--your clinical relapse could be the result of a new organism. So

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I guess I would agree. To me, relapse sounds like it is the same thing has come back. So, to me, the clinical should also be called recurrence.

DR. RELLER: The beauty of the recurrence is historically, clinically and every other way, it does not imply, necessarily, that you know or that you are certain or anything else whether it is the same organism or a different organism. The patient just is symptomatic again or an organism is there again.

I think there are a lot of changes being made and this is an opportunity to change that, when it comes back again, clinically or microbiologically, it is a recurrence. Then, whether or not it is new infection, or it is a recurrence with the same infection heretofore called a relapse, that that would require microbiological evidence of a difference, be it different genus and species or different by molecular typing techniques that are so much easier and cheaper and more readily available than the old serotyping that was not done because it was too problematic.

DR. ALBRECHT: As far as the issue of serotypes or strains and so forth, again, I think, whether this is right or wrong, it is sort of a regulatory approach because when we approve drug products for, let's say, urinary-tract

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infection due to E.coli, we never talk about which strains were or weren't or serotypes of other organisms and so forth.

It is simply that we mention the genus and species and, therefore, on many occasions when patients are evaluated, there is an E.coli before, there is an E.coli after. And you are right, Dr. Murray, we do not have always the information on whether it is exactly the same organism.

But, again, because the drugs we are approving, we mention the genus and species, this has sort of been a tradition that we have had.

DR. MURRAY: But keep in mind that it sounds like you are using a terminology that is not the same terminology that is used by the general infectious-diseases community. So I think that needs to be kept in mind because we are all thinking of recurrence as a more general term. You divide those into relapse and new.

We can debate whether or not you need to do this or whether or not it is important, but it sounds like you are using a sightly different terminology than the way we usually talk about things. That could get into logistic--

DR. MURPHY: I think that is important and I think we should pursue this just a minute more because if we look,

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we have five micro outcomes and two clinical, two or three. If you would, at the four-to-six weeks post-therapy, we have sustained for clinical failure and we are talking about relapse versus recurrence.

At the four-to-six-week micro, we have sustained, persistent, superinfection, recurrence and new infection. I think that we would like to hear the committee's comments on how they feel those would be best categorized.

DR. CRAIG: As I said, to me, the relapse that you have for clinical is really recurrence because you don't know what it is. For microbiologic, what you call recurrence, by your definition, is really more relapse. And then you have got new infection as your other opportunity. So it is sort of the reverse of what you have.

DR. MURPHY: So, for the micro, how would you reshuffle those, or would you--those five?

DR. CRAIG: Recurrence would be called relapse.

DR. MURPHY: And new infection would stay new infection. Superinfection would stay superinfection. Persistence would stay persistence.

DR. CRAIG: Those, superinfection would be the same.

DR. MURPHY: And persistence?

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DR. CRAIG: Persistence? In a way, persistence is relapse. What you are trying to do is have a relapse that occurs after something has been clean for a period of time and trying to have a nomenclature for that, a separate nomenclature for that.

The problem of using recurrence for it is that is just a more general term. It is sort of like a late relapse.

DR. GOLDBERGER: There is, I guess, a question of changing the wording to reflect the uncertainty of what we actually know or making an effort within the clinical trials to actually get more information to reduce the uncertainty. That is, obviously, going to increase the resources required to do clinical trials.

It would be interesting to hear how important that is to people on the committee versus simply changing the wording to reflect some of the uncertainties.

DR. RELLER: That is why I favor, clearly, the first one clinically being recurrence because that captures all of those that either come back or are new. They are sick again. But, Bill, it says of the original uropathogen, but we recognize, under the usual circumstances--in fact, maybe fairly often--there is not, with genus and species,

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the ability to be absolutely certain of that.

But without further--you have to call them--they are a recurrence of the same organism, what appears to be the same organism, but, in fact, it may be a new one if one further looked at it.

So why not keep that term more generic rather than implying a specificity that is not there.

DR. CRAIG: I have no trouble with that.

DR. RELLER: Maybe it would be easier to get the agency to reconsider the terms of they aren't just flip-flopped. You have two, but keep the generic one. Is it possible to change? Is this something that is in the Federal Record that you have to do it this way?

DR. ALBRECHT: The obvious confusion is going to come up if somebody requests something through FOI and they are looking at a document which says recurrence, and then they will have to see what year it was written as to what the term meant.

DR. CRAIG: So the primary thing, to summarize what he is saying, is the only thing that needs to be changed is relapse to recurrence under clinical.

DR. MURRAY: And under microbiologic, new actually fits under recurrence

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DR. CRAIG: No; I think what I heard Barth making was the only change should be relapse under clinical should become recurrence.

DR. RELLER: You are absolutely right, Barbara, that a new infection is in the generic sense a recurrence. The only difference is microbiologically here you know that it is a different organism because it is a different genus and species whereas in the recurrence one, some of that would include those that are truly the same and those that are different.

It is just that one can't make that distinction because you haven't got the data whereas the new infection--this is sort of a subset of those recurrences where, because it happens to be a different organism altogether, one can go ahead and establish that it is really a new infection.

DR. CHESNEY: Could I ask for just a point of clarification. Why is the test-of-cure done after the antibiotic has been stopped for five-to-nine days? I assume that is a definition that is well understood in the adult literature. Why isn't it done during therapy?

In other words, would it not be possible to have--

DR. CRAIG: The presence of antibiotic may

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interfere with picking up the organism.

DR. ALIVISATOS: You don't want to have any drug on board, in other words. It is half lives. It can be, how many, five half lives or five-to-nine days. It all has to be done. And some of the newer agents have longer half lives. So it goes out to about five days.

DR. CHESNEY: Wouldn't it be possible to have a cure during therapy and then a recurrence within five days, or whatever we are calling it now, within five days of stopping the antibiotics?

DR. ALIVISATOS: You could not have a cure during therapy because you still have the effect of therapy ongoing. So you have to be finished with therapy in order to see if it worked. You can have a patient that is doing better on therapy.

DR. GOLDBERGER: A positive culture late on therapy would naturally not be a good thing. But a negative could not be interpreted until it is repeated after antibiotic is gone.

DR. ALBRECHT: Independent of the terminology, whether we say cure at one time point or another, I guess what I would like to ask is are we implying, then, that we don't need to see the patients after we would designate them

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a cure.

In other words, I think what we have thought is when you say "cure," that means you have gotten to the ultimate endpoint. I don't think any of us have believed that an on-treatment assessment is getting to the endpoint. We believe that you need to be off-therapy to determine whether or not the organisms were simply suppressed and have now come back in culture.

So I guess I would ask when you mean the on-treatment designation of cure, is that synonymous with an endpoint.

DR. CHESNEY: I don't want to complicate issues but I was just thinking, meningitis being an analogy, we would assume that a negative culture on-therapy meant a cure and that, if the patient came back five days later, that it would be not that they hadn't been cured the first time but that they had reacquired an infection.

I am probably not expressing myself very well, but--

DR. MURRAY: But, in meningitis, the concentration is usually so much lower whereas, in the urinary tract, for so many of the drugs, the concentration may be hundreds of times the MIC so that even a dilutional effect onto agar may

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not be sufficient to remove the antibiotic whereas in the CSF, you are going to be marginally above, usually, the MIC.

DR. CHESNEY: So it is a microbiologic kind of phenomenon?

DR. RELLER: The cultures on therapy in these patients, even the most complicated ones, assuming that there is not a total obstruction, they are almost always negative by the usual techniques unless you have missed it so far that the organism was not susceptible which one would have known.

If the patient is putting out urine and they are getting the drug, and the organism isolated initially is susceptible to the compound that would be a requirement for the trial, the culture on therapy is going to be negative, which reminds me of one of the things that figured prominently in the discussion about these endpoint criteria for interpretation of the different categories is part of that package was the great support for the follow-up cultures out at four-to-six weeks to address the issues of these people who were in the ambiguous area that a minority of them would declare themselves by that time into one of these categories.

That is sort of a safety feature for the

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difference between the simpler acute pyelonephritis that Dr. Soper was concerned about and the other patients with stones, obstruction and so on that triggered their acute complicated urinary-tract infection.

DR. CRAIG: Are there other issues? We have got, at most, five minutes to stay on time.

DR. WITTES: I have an issue but I could bring it up at a different time.

DR. CRAIG: No; we have five minutes. Go ahead.

DR. WITTES: It is totally predictable. It has to do with the exclusive focus on the evaluable patients. I understand that, in this case, the evaluable means fully compliant with therapy.

Can I put up an overhead?

[Slide.]

This is clearly a recurrent theme, to use the words of the--okay; this is my picture. This is why this kind of analysis worries me especially when it is the only analysis.

Imagine that that big circle is the population of the study group that is going to be randomized. Imagine that there is a subgroup that is destined to be nonevaluable for treatment X and a subgroup that is going to be

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nonevaluable for treatment Y. Those are, presumably, overlapping.

Now, clearly, the more overlapping there is going to be, the less of a problem we are going to have. So I made them deliberately not very overlapping. You then randomize into treatment X and treatment Y. Assuming your sample size is large enough and so forth, you have the same distribution of these ultimately destined-to-be-nonevaluables in the two groups.

Those two circles, that big rectangle thing, that is the randomized comparison that you have got and that is what randomization did for you. It allowed you to compare two groups that were equal at baseline.

You now have those in X who become nonevaluable drop out, and those in Y who become nonevaluble drop out, leaving the bottom circles, and those little non-circle things represent those destined on the left--those destined to be nonevaluable for Y exclusive of those who had been nonevaluable for X because they dropped out because they were on X.

Similarly, the group on the right-hand side.

This comparison which is the evaluable comparison, is no longer protected by randomization and the degree to

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which it is not depends on the size of those nonevaluable groups and the difference between them at baseline.

So it seems to me that to call a study that looks at that bottom line a randomized, well-controlled study--it is not. What was randomized and well-controlled was the level above. There are, obviously, very good reasons to be making the comparison down there but it is a very different kind of comparison and it seems to me that whatever analysis is done at that level needs to acknowledge very explicitly and probably statistically and mathematically that there are imbalances there.

So at least, it seems to me, that in any of these guidances, there needs to be some provision that there be an analysis at the level that was, in fact, protected by randomization and that there be a sample-size calculation that is large enough so that that comparison isn't totally muddied by the nonevaluables.

That comment will go--I won't make it again. That will go for all of the tabs.

DR. CRAIG: Do you want to respond to that?

DR. LIN: Yes. Daphne Lin. I agree with Dr. Wittes' comment. I think we need to do both intent-to-treat and per-protocol analyses. If there is a discrepancy, then

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this is the place, because yesterday I mentioned, we would like to have a table to describe if the patient is excluded from the intent-to-treat, we would like to know the reason.

So I think all of these tables can explain the situation you just mentioned.

DR. WITTES: No; I was very comfortable with the presentation but that spirit isn't in all the guidances. I am just urging that it get incorporated.

DR. MURPHY: And we want you to not keep quiet. We want you to bring that up. As you know, we have mentioned, these guidances are dynamic and they are changing. Some of them are in various degrees of change. The answer is yes, we change. We have to deal with all the problems that result from those changes so we try to make sure we change when it is absolutely to the benefit of both the patients and the science, if you will.

I think that this is a perfectly good example because compliance can tell us something more than the fact that the patient didn't take the medicine. We have to be very careful about just saying that compliance makes them nonevaluable or noncompliance makes them nonevaluble. It is just one of the issues.

DR. CRAIG: Any other comments? Any other

questions that the FDA would have on this topic?

DR. MURPHY: Let me just get back--let's be radical here. What would the committee think about taking all the microbiologic criteria and, instead of having five, we have sustained eradication and failure. And, under failure, we have other categories. I am just throwing it out for that possible discussion.

DR. CRAIG: Personally, I think you can know more than just failure. I think it is useful to know about a drug, whether it results in a high degree of superinfection. So I think that is clearly one of things that you want to keep there.

DR. MURRAY: Except that we are so limited because we are only to show its superinfection or new infection when it is a different genus and species, which most of them won't be. That is why your terminology either has to account for that or you have to do what Barth suggested.

I am not advocating necessarily one or the other. It is just that you are implying that you are able to do something here that you are really not doing because other than the baseline pathogen, if it is another E.coli, you don't know that, there's another strain.

You can only tell it is superinfection when it is

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a different genus and species because if it is another E.coli, you can't, with certainty, unless you do typing, know that it is a different E.coli. So you can't distinguish persistence from superinfection without doing typing.

That is my basic problem. It is more of a problem with sort of terminology and the implications that you are doing something that you can't.

DR. CRAIG: But even though you are not as accurate, and the sensitivity in picking it up is not sufficient, it does help you break up failure somewhat. So it does give you some additional information.

If you saw loads of patients being colonized with, or getting infection with, Candida, with the use of this drug, that would be useful information as compared to not seeing that with the comparator. So I think, by breaking it up and not just calling it failure, even though it is incomplete in how you can break things apart, it is still useful.

So I would not be for just calling it failure. I am open to the other members comment.

DR. MURPHY: We would like to hear what others think because I think that what we are saying is--and the

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terminology is not set; I'm just trying to get the concept out--we have sustained eradication versus failure. Under failure, you describe how they fail. Does it make a difference and how does it make a difference in whether the drug is effective under failure? That is what you are trying to get at.

DR. CRAIG: If you are comparing two drugs, and for one drug, you get a lot more of what we are calling persistence, and not being able to use it, but you don't see that with the other drug, I would find it hard, in a randomized trial, to expect that what you were seeing in one group was the unluckiness that they were all the same organism and, in the other group, it was a different scenario.

So I think, knowing some of those differences between drugs gives you some idea about the activity of the agent. It is going to be a failure, but why is the drug failing? Is it failing because it doesn't get rid of the organism that is there or is it failing because of the fact that it frequently results in superinfection.

So I think at least I do get some information from spreading it out a little bit here as to a little bit about what is wrong with the drug in terms of resulting in

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failure.

DR. SOPER: I think you have to be descriptive, I think is what you are asking. There are only so many scenarios here; right? Everybody is positive going in and give you an early culture. Some of those are going to be positive. Some of those are going to be negative. Then the late culture; some of those are going to be positive and some of those are going to be negative.

Some of those are going to be different organisms and some are going to be the same. That is what you need to essentially put a word to and describe. I don't think it makes any difference what you call it. I would call it what we have pretty much been bouncing around here because we are used to that kind of terminology.

But that is the information that we want when we look at these kinds of studies. It needs to be present in the work that is submitted. What we call it is up to you, as far as I am concerned.

DR. NORDEN: I think that is right. I think that when you use the term "superinfection," you are implying more precision than the data that we have obtained gives us. But if you tell us, or if it is available, that, of those patients who failed, 20 had the same organism as noted by

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genus and species but they were 40 isolates of Candida and 20 of coagulase-negative Staph, that is very useful information and helps you in terms of thinking about a drug.

So I am perfectly comfortable with the term "failure" as long as, under the failures, we know what--

DR. MURPHY: That is what I am asking. Instead of going from positive, everybody's positive, to negative-positive, what is here is you go to negative and then you have five other categories. Do you see what I am saying? It makes a difference in the cells.

DR. CRAIG: It's where you want to call a late new infection a failure of the initial drug, where you had the organism to treat, you treated that organism at your test-of-cure time. The urine was negative and now, four-to-six weeks later, we now have a new organism that wasn't present before.

I am not convinced that I would necessarily call that a failure of the earlier drug.

DR. NORDEN: I wouldn't either, but I thought the test-of-cure, which was the earlier--

DR. CRAIG: No; these five are based on the four-to-six-week evaluation.

DR. ALBRECHT: You are correct, Dr. Craig.

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Historically, when we have looked at urinary-tract-infection studies, we base our regulatory decisions on the outcome at the five-to-nine days. It is simply because of the natural history of what happens to patients that we have encouraged companies to pursue the four-to-six-week follow up.

We get, sometimes, about a 50 percent follow up of the original patients to determine whether or not there are any differences in the long term between patient outcomes. But our strict sort of cure, failure, eradicate, persistence terms are applied and decisions are primarily based on the test-of-cure five-to-nine-day visits.

DR. CHESNEY: I would vote for keeping the terminology there. I think it is very clear. I think what I am hearing and I would share the discomfort that Barbara has that, if you have an E.coli as your original agent and then you have E.coli isolated subsequently, you don't know that it is the same E.coli. I think if there were some way to do pulse-field gel electrophoresis, or whatever, to identify whether it is a new E. coli or the same E.coli, that would make me comfortable with the terminology that is here.

I think that is what I heard Barbara saying.

DR. RELLER: Why not just describe, up at the top,

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that all of these--and I think that they serve a useful purpose, both for delineation and that some of them are employed early on and some late on to capture what has really happened after therapy in these patients.

But why not just have a statement up with the microbiology to say that all of these designations are based on customary genus and species designation unless additional data are provided or something like that.

DR. ALTAIE: I have one suggestion. We could go ask for the molecular diagnostic pulse-gel electrophoresis which is the cheapest one, most available one, at this time. It will serve the purpose. And put it out there, see the comments from the industry, how much opposition do we get at this time when the technology has moved so much forward. And see what happens.

If we don't get cooperation, then we are back to your suggestion.

DR. CRAIG: At least my thinking is that the company would do it if is would make their drug look better or to try and explain why their drug looked worse, to try and make sure that if they were looking like they had more persistence, I think that it would be an incentive for them to do it.

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On the other hand, if there is no difference, I don't know why spending extra money to try and refine it a little better is going to be of any value.

DR. MURRAY: I tend to agree with that. I, personally, would probably be happy with Barth's suggestion as long as when you say "original uropathogen," it is clear that you cannot say that with accuracy. If that is just clarified, explained, put in parenthesis, based on the limited differentiability using genus and species or something like that, I would be content.

It is just that the way it is written, it is implying a great deal of specificity that you don't have.

DR. ALTAIE: That's fair enough.

DR. GESSER: Richard Gesser from Merck Research Labs. Functionally, superinfections or persistence are both failures, according to the definitions, so you are not required to do that type of molecular analysis in order to determine whether a patient is a failure or a cure, according to the guidelines that you put here.

The other point is that persistence is an imprecise terms for the same reasons that you mentioned as well. I guess the only place where, perhaps, molecular characterization really would change whether a patient was a

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cure or maybe indeterminant or a failure would be at the test-of-cure visit when you are trying to define, for example, new infections which I have heard should not be scored either failures or cures but may make a patient indeterminant for one reason or another.

So I would agree with the comment to specify exactly what is being stated there rather than the request because of the other issues, too, that sites will never do this. It is really something that you rely on samples being sent back and either the sponsor or a third party doing it to determine the outcome. I think there is a certain risk involved in that.

Certainly, I think, we'll be interested in isolates at the test-of-cure that could fall out as either cures or failures depending on specific analyses. But, during therapy, I think there is no functional distinction between those things.

DR. CRAIG: Any other comments?

DR. HENRY: We keep talking about all these terms from very broad terms to cure and failure to very specific terms. But, again, even using specific terms isn't very helpful if we don't have the accurate microbiology. Historically, we are told that these terms were used and

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people are comfortable with these in terms of reviewing drug studies.

But, historically, we didn't have pulse-field gel electrophoresis. So if we are going to bring these terms into present-day terminology, we should be using present-day microbiology in order to make the most out of what we are really talking about.

So I don't know how you can say we can play around with the terms without really updating what is required of the microbiology for this to substantiate what we are really talking about.

DR. ALTAIE: I couldn't agree more.

DR. SOPER: Particularly in this scenario where you are talking about a very limited number of patients. You have already said that one of the reasons why you don't have two RCTs here is that there are not that many patients to study. So the overall cost to industry for this I think would be relatively limited.

So I would endorse this request for improved identification of the pathogen as well.

DR. CRAIG: Any other comments?

DR. MOONSAMMY: George Moonsammy, Smith-Kline Beecham. I just had a question regarding classification of

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a patient who is a bacteriological cure at the five-to-nine-day visit. There are some patients may come in with clinical signs and symptoms so they may be considered a clinical failure.

How would you classify this patient when, at the test-of-cure visit, the urine specimen shows less than 10^4 to the organism but the patient may still have some clinical signs and symptoms of infection?

DR. ALBRECHT: Bacterial eradication, clinical failure.

DR. CRAIG: In, in reality, it could even be, in real life, a bacteriologic failure being one of those people that have smaller numbers of bacteria. But with the nomenclature that we would have , you would have to call it bacteriologic eradication.

Let's, then, move on to the next topic which Dr. Albrecht will be doing on the general guidelines.

General Clinical Considerations

FDA Presentation

DR. ALBRECHT: Thank you, Dr. Craig.

[Slide.]

This morning, I would like to review some of the highlights from our guidance document on developing

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antimicrobial drugs, general considerations for clinical trials, particularly focussing on the clinical sections.

[Slide.]

As I mentioned yesterday, in the series of eighteen documents, we have one overview document called the Developing Antimicrobial Drugs, General Considerations for Clinical Trials which is divided into multiple sections. Yesterday morning, you heard Dr. Daphne Lin talk about the biostatistical section. Tomorrow morning, you will hear Dr. Altaie present the microbiology update, Dr. Osterberg talk about the pharmacology-toxicology update and Dr. Colangelo review some of the clinical pharmacology new issues.

Today, I will highlight the clinical sections. In fact, as we mentioned, sort of in planning the agenda, why didn't we cover the whole document all in one day, we, in a sense, divided it in reverse order of degree of revision so that, as you heard yesterday, some of the newer concepts compared to our old documents were presented in biostatistics section and now, today, I will highlight some of the proposed revisions and updates in the clinical section.

I am almost scared to have the next slide come up.

[Slide.]

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As is stated in the introductory section of the general considerations document. It is the intent of ODE-4 also this is addressed in the Federal Register notice of July 21, it is the intent of ODE-4 to take all existing guidance documents or guidelines that we have and take all relevant information and put it into these new guidances.

So, as you can imagine, the information from the 1992 point to consider document, the 1997 guidance document, has been incorporated, modified and revised into the currently proposed guidance documents.

Therefore, it would seem to follow naturally that the focus from the previous guidance on evaluability criteria has now been expanded more to a total drug-development concept.

[Slide.]

In keeping with that and, I think, as we have heard in the previous day or so, there is a great deal of difficulty interpreting clinical trials where there is a lot of missing data and where we end up having a lot of patients that we can't figure out what to do with and we end up calling them unevaluable.

As Dr. Wittes pointed out, there are certain pitfalls when you start doing those kinds of things. So we

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are focussing back to the early part of the process and realizing that protocol planning, protocol design and protocol implementation are really key.

I think we have always known this. We are just restating it again. Another way of stating that is that a clinical trial is only as good as the protocol serving as its foundation and so our current document spends a good deal of time discussing the importance of good clinical protocols.

[Slide.]

Basically, I think we all recognize a protocol should be a template or a recipe, if you will, for a clinical trial. It should have a clear purpose. It should have the procedures clearly spelled out and it should have easily obtainable endpoints.

The protocol should be responsibly conducted and there needs to be good monitoring.

[Slide.]

In addition to a good protocol, we also have sections in the current general guidance document addressing, in brief, supporting documents such as the case-report form which, as we all know, is the record of what was actually done, what procedures the patient had, et

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cetera. And we also recommend, in this era as we are moving toward electronic submissions and electronic review, that that case-report form be annotated early on for electronic submission so that there is a clear link between the data points captured on the case-report form and the data elements as they are identified in the ultimate database.

Finally, a consent form is also important. There are regulations. The Code of Federal Regulation, of course, talks about the elements of the consent form, but we look for it to see what kind of communication exists between the investigator and patient that the risk-benefit of the study has been addressed and discussed with the patient.

[Slide.]

Now I am going to try to discuss and respond to some of the comments that we received from industry in response to our original 1997 guidance. There was a question about blinding, what happens when you can't blind.

Just to review, of course, blinding is very useful in preventing bias in randomization and so forth. We do, of course, recommend double blinding whenever possible.

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But there are circumstances where double blinding is not practical or feasible. In those cases, we would

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encourage the industry in the protocol to address how non-bias will be assured. So what are the options? Is there a third-party blinded? Is there a laboratory endpoint and, therefore, the laboratory can be blinded?

There is a unique situation where we have non-comparative or what we have called before open trials where the drug regimen assignment is known. In those scenarios, the agency recommends a registration log of the patients that were screened for entry into the study and the ones that were ultimately selected.

Again, this is an effort for us to understand that there was no bias introduced.

[Slide.]

As far as inclusion criteria, some general comments. In information on inclusion criteria, of course, is detailed in each of the companion guidance documents and you have heard many of those already presented and you will hear the rest in the next day and a half.

[Slide.]

I commented yesterday on this topic, and let me just briefly comment that the terminology we have used, in talking about clinically driven study, is where we rely on the signs and symptoms of the disease both at entry and at

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the test-of-cure endpoint.

Clinically and microbiologically driven studies are one where we have microbiology but it is available at baseline. We do not routinely ask for microbiology at the test-of-cure visit simply because either the specimen is not available or it is too traumatic, examples being meningitis or pneumonia.

Finally, what we refer to as microbiologically drive studies; this means that cultures for the microbiology of the microspecimen are obtained both at entry and at test-of-cure. That is not to imply that we don't also look at clinical signs and symptoms in these patients.

[Slide.]

The general considerations document discusses exclusion criteria. It is recognized that there are some that apply to all clinical trials; for example, hypersensitivity to the drugs under study would be a reason not to include a patient, recent antimicrobial use, confounding diseases and baseline abnormalities which make it difficult to evaluate the role of the antimicrobial in the patient's course.

Of course, specific exclusion criteria have been commented on by the individual presenters and will also be

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discussed later which are present within the individual companion documents for the specific indications.

[Slide.]

Drug selection and dosing; the document makes general comments about the study drug, control drug and concomitant medication. Basically, as far as study drug selection, of course, it advises that information from in vitro microbiological results, pharmacokinetics, pharmacodynamic studies, and the disease under study be taken into consideration in selecting the dosage regimen.

[Slide.]

A few comments on the control regimen. Ideally, of course, and the simplest, would be to use a control regimen that is approved by the FDA. There are situations where this is not feasible and, in those, we would strongly encourage the industry to call the FDA and discuss the matter.

Some examples include there is no comparator approved as we are facing now with vancomycin-resistant Enterococcus. There is a community standard that is used but it is not FDA-approved. Or the drug to be used is approved for a different regimen than the company would propose to study it at.

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It is important to document the use of concomitant medications. They may modify or mask symptoms of the disease. They may have their own attendant adverse events that need to be recognized. We are particularly interested in looking at clinical studies on the use of any other antimicrobials, those specified in the protocol and, certainly, if ones are used that are not specified in the protocol.

[Slide.]

A few words about evaluation visits. There are, as you have noticed during the preceding day and you will notice later, a number of visits that patients are asked to participate in. But I think the general tenor that we are proposing now is that, very importantly, we would like to have baseline visits and the data from those on all patients and then have data on the test-of-cure visit which, depending on the indication, occurs a few weeks or a few months after the completion of therapy.

We are recognizing that it becomes difficult to ask patients to come to many intervening visits and so we consider them, in many cases, to be optional. You heard yesterday some recommendations that you can substitute telephone contact for those.

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So this is an attempt to try to make it more practical to gather the critical data.

[Slide.]

You will have noticed that our current document not only discusses sort of adult studies in general but has specific sections addressing pediatric patients, geriatric patients and pregnant patients. I think these initiatives are certainly in keeping with the FDAMA revisions and, certainly, are ones that we recognize as being important.

[Slide.]

We had a comment from industry about when you are asking for all the data, does that mean the reviewers are going to look at every single data point and do all these complex analyses. Clearly, that is not the intent of a review.

The purpose of a review is not to validate and examine all the raw data and perform all the analyses specified in the protocol.

[Slide.]

But, rather, it is to make an independent assessment that the clinical protocol was implemented correctly, that the requested data were collected and documented, that the analyses were appropriate and that the

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results do provide information on a drug's efficacy and safety.

[Slide.]

This is the issue of which populations do we look at. Certainly, we are proposing, perhaps, that, instead of having one population, we should be looking at accounting for the patients from randomization down to a per-protocol population looking at the clinical outcome and microbiologic outcome.

[Slide.]

We are proposing, in most indications, to look for a dichotomous outcome of cure or failure. In general, individual presenters have given you the definitions for these terms within the individual companion documents. But, in general, the idea is that cure would refer to a resolution of the acute presenting signs and symptoms of the disease and no additional antimicrobial use in that patient because, in fact, what the purpose of doing these studies is is to assess whether the drug under study is effective in the given indication.

Then, failure, depending on the specific indication, is simply someone who was not cured.

[Slide.]

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We did receive a comment about the utility of the term "improvement" and could we keep that in as one of the outcome categories. We recognize its usefulness as an interim assessment, if you will. The patient is improving; therefore, we continue them on therapy and so forth.

However, it becomes a little more treacherous when we use the term and, as was proposed at the test-of-cure visit because, what is improvement, how much improvement. Does it really show the drug is effective or that the patient just gets better over time.

Improvement; do we know if the patient will need additional antimicrobials. Then, perhaps, the original drug was not successful and we shouldn't be calling it improvement. If a patient is termed improvement, is that simply a slower response? Is that something indigenous to the patient?

So we recognize that this may be useful during the on-treatment visits but propose not to use it as a test-of-cure term.

[Slide.]

There is also some difficulty when it comes to using the term "improvement" as far as promotion. If we have drugs, as we do some of the older ones where cure and

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improvement rates are reported as successes in the labeling, higher rates are reported in these older drugs. Then, if we now talk about a dichotomous outcome with cure only, then there are lower rates reported in the label.

Certainly, this is a topic that is well-known to us and to DDMAC. And we believe it is only fair to work out clear definitions so that there is appropriate promotional balance.

[Slide.]

There was a question raised about what do you do about follow-up test-of-cure visits when you are comparing two drug regimens of differing durations. By way of example, let me just address that assuming that we have a study where you have a single dose being compared to a seven-day regimen.

It is not so far-fetched because, as we heard during the discussions yesterday on topics like vulvovaginal Candidiasis and bacterial vaginosis, companies are developing drugs for different durations. If, given this particular kind of scenario, the test-of-cure, let's say, usually would have been stated as five-to-nine days after the completion of therapy.

We now recommend a conservative approach which is

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to say that we would recommend a test-of-cure five-to-nine days after completing the longer course of therapy which would translate into study day 12 to 17. As you noticed, and have noticed, in many documents, we actually now talk about the test-of-cure relative to the start of therapy.

The rationale for this kind of approach is that the convenience of having a shorter regimen shouldn't compromise the long-term benefit to the patient.

[Slide.]

In our document, we talk about documenting what the patient's course is at the time that the patient is switched from parenteral IV therapy, let's say, to oral therapy and a request was made that we give further guidance.

This is a complicated area and it continues to be under discussion, so we do not, at this point, have more specific guidance. But the idea is that some objective criteria should be consistently followed, that there is enough information obtained from the patient at that transition period so that it is possible to determine the contribution of the parenteral therapy as well as the oral treatment.

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This topic came up yesterday and we were also asked, of course, in the comments about the acceptability of foreign studies. Actually, the Code of Federal Regulations tackles this topic and it discusses the acceptability of foreign data. Foreign data, of course, is acceptable to support approval of an agent in the U.S. with the following caveats.

The information submitted from the foreign studies should be applicable to the U.S. population; that is to say, the patients enrolled, the organisms studied and the diseases should be ones that are also found in the U.S. In addition, the studies should be conducted in the manner and have the same quality as any study conducted in the U.S. and then, importantly, the agency does need to have access to the patient data so the Division of Scientific Investigations may actually go and review the quality and completeness of such data.

[Slide.]

Finally, there is a section in the current document which was incorporated from the points and expanded on approval and labeling, specifically talking about information to be included in the indication and usage and microbiology sections.

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[Slide.]

With that, I will conclude my remarks and ask if there are any questions.

DR. CRAIG: Any questions? Dr. Chesney?

DR. CHESNEY: This is more of a comment which has to do with the control drug or the comparator drug. Just to emphasize, particularly for otitis media, for example, there is some feeling out there that it is easy to choose a comparator drug that your drug is going to look good against.

If there were some way that you all could talk to companies about what is a good comparator drug for this particular study.

DR. ALBRECHT: You have identified an area that we have tackled with for a long time and, in fact, in many of these studies of otitis and other indications. We do try to advise companies to use regimens that are relevant to sort of the current status of patients and conditions.

However, we have also learned that sometimes the choice of the comparator is based on the market; who are the competitors, whom do they have to test themselves against, what information physicians want to know as far as how does it compare to one regimen or another.

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So it is a fairly complex issue, but if there are any sort of specific suggestions on either issues that we should tackle or drugs that--you mentioned three yesterday--that we should recommend, that would be helpful.

DR. CRAIG: I guess the whole question comes up again with meningitis that we talked about before, what is an appropriate comparator, especially now in the United States. It almost is a cephalosporin along with vancomycin for pneumococci. Even tough the organism would be resistant to one of the two agents, at least the clinical experience with that regimen has been excellent.

So it makes coming up for, as we said, a trial, if you had a new cephalosporin that you wanted to get approved for that, it could be a real problem trying to design a study where you would be just looking at the drug alone.

Any other questions, comments?

DR. KIRK: Cindy Kirk from Hoechst-Marion-Roussel. I was interested in knowing, regarding foreign studies as the basis for U.S. marketing approval, does the FDA require that these studies be filed to or conducted under the U.S. IND in order to be considered adequate and well-controlled?

DR. ALBRECHT: It is a lot easier if they are conducted under IND. We actually do have experience with

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companies that have filed an IND and they propose to do one study in the U.S. and a very similar study abroad. If they are not filed under IND, they may also still be acceptable. However, because we are the FDA, we will have the same kind of requirements of consent forms that are written and how do you, then, determine whether, in fact, the patients were enrolled appropriately if we don't have written consent forms and simply have some verbal declaration of Helsinki compliance.

The same problem arises--we have had scenarios where investigators in foreign countries have said, "I'm not giving access to my data." If, up front, they are participants in an IND, then this has all been discussed with them early on and it doesn't become an issue, and our DSI staff wants to go to inspect a site and are told, "No; sorry. We can't give you access."

So I think it is a practical matter to try to plan this at the IND. But, if is not, simply, it would important that all the points that I have raised are met and then the information can still be acceptable.

DR. KIRK: Thank you.

DR. FOX: Barry Fox, from Bristol Myers. Has there been any discussion regarding an attempt to

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standardize the allowed duration of prior antimicrobial therapy? For example, in the 1992 IDSA guidelines, if the anticipated duration of antimicrobial therapy was to be seven-to-fourteen days, the IDSA guidelines recommended up to 24 hours of prior antimicrobial therapy.

Perhaps, this is an issue that will be addressed for tomorrow morning, but has the agency given consideration to providing any kind of standard operating procedure for prior antimicrobial therapy?

DR. ALBRECHT: We have thought about it, but it just an extremely difficult area, as you can imagine. The basic concept behind this is we are evaluating new antimicrobials for their role and their effectiveness in treating infections.

So, in the ideal world, the patient would have seen no antimicrobials within, and we can all debate whether it is 24, 48 hours or a week, but that this patient would not have any antimicrobial effect, be it post-antibiotic and so forth, when the test drug is being evaluated.

We recognize, however, that from a practical perspective, that is just not how it happens. I think what we are learning now is that, in a sense, we almost have to consider it on a case-by-case basis. In the protocol, we

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hope that the sponsor addresses how these kinds of patients who have had recent therapy will be handled.

For example, with resistant organisms, very often what happens is you have patients that have received one antimicrobial and now the company proposes to roll them over, if you will, into a study of a new antimicrobial. An organism is isolated. It is resistant to the previous drug. It is susceptible to the current drug.

Clearly, we want to get the information on that kind of patient. So I think, at best, we can say it is case by case as far as the study and, certainly, if anyone can help us have some really standardized approaches, that would be valuable.

But I think it is admitting it up front, how much antimicrobial is being used and trying to interpret the information in context.

DR. FOX: Thank you. That was helpful.

DR. CRAIG: I think the problem also occurs nowadays with some of the antibiotics being so potent and rapid in their bacteriocidal activity that there are sterilizations occurring within a few hours. So that makes prior antibiotic therapy a concern.

But with the old, slower-acting drugs, it was

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easier to tolerate some antibiotic therapy prior to entering the study.

DR. ALBRECHT: Exactly. When the IDSA guidelines came out and said, "Well, if you are planning a ten-day course, a single dose is okay." But if we think about urinary-tract infections and the changes that we have gone through, now single doses actually treat the infection. So time changes a lot of our basic concepts.

DR. CRAIG: Are there any other comments?

Then I guess we move on to the next one which is bacterial prostatitis. The FDA presentation, again, will be by Dr. Alivisatos.

Bacterial Prostatitis

FDA Presentation

[Slide.]

DR. ALIVISATOS: Acute or chronic bacterial prostatitis. I would like to point out that the title of this section is Acute or Chronic Bacterial Prostatitis. As you may or may not know, this is different from what was in the 1992 points to consider document which referred only to bacterial prostatitis and did not differentiate between the forms of the disease.

In the next 20 minutes, I would like to go over

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this indication.

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A review of the current literature reveals that the clinical entity of prostatitis can be divided into four clinical syndromes; acute bacterial prostatitis, chronic bacterial prostatitis, non-bacterial prostatitis, and prostadynia.

The current classification system that is primarily used is that of Drach et al., and the entities are separated based on chronology, severity of symptoms and the presence or absence of leukocytes and/or bacteria in the various segmented urine cultures and the prostatic secretional cultures.

This classification system is widely used but it has never been validated and there appears to exist a lot of confusion within the field or fields as to the accurate diagnosis and classification of the classification entities of prostatitis.

[Slide.]

Because of this, the NIH has a consensus conference on prostatitis and, in 1995, they published a new classification system that divides prostatitis into four categories.

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The first two categories are essentially what we are talking about today. Category I is acute bacterial prostatitis or acute infection of the prostate gland and category II is chronic bacterial prostatitis or recurrent infection of the prostate gland.

Again, both of these categories are defined by the presence of pathogens--bacteria, in other words--cultured from a specific urine and prostatic secretion specimens.

[Slide.]

There are also two other categories; category III which is chronic abacterial prostatitis or chronic pelvic pain syndrome where there is no demonstrable infection and this is divided into IIIA which is inflammatory and IIIB which is non-inflammatory, and category IV which is asymptomatic inflammatory prostatitis.

The use of this system is becoming increasingly prevalent.

[Slide.]

To illustrate some of the confusion that exists in the classification of the various clinical entities of prostatitis and the difficulties that, then, occur in labeling, I would like to quickly point out the indications that have been received by four quinolone antimicrobials

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within the past eight years.

Ofloxacin in 1990 received the indication of bacterial prostatitis caused by Escherichia coli. Norfloxacin in 1992, prostatitis caused by Escherichia coli. Ciprofloxacin in 1996, chronic bacterial prostatitis caused by Escherichia coli and Proteus mirabilis. And trovafloxacin in 1997, chronic bacterial prostatitis caused by Escherichia coli, Enterococcus faecalis and Staphylococcus epidermidis.

As you can see, the earlier approvals adhered to the language in the points to consider document or what was used at the time. However, later approvals have become more specific in describing the patient population that was studied.

Before proceeding, I would like to point out that the 1992 IDSA FDA guidelines do refer to prostatitis within the context of the complicated urinary-tract indication. However, these guidelines did provide for a modified trial design for this entity and modified evaluability criteria.

The divisions agree with this stance because of the more prolonged duration of therapy that these patients need in conjunction with the more complex diagnostic testing.

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[Slide.]

The differentiation of prostatitis into acute and chronic is clinically and microbiologically driven. I have used Dr. Kunin's definition. "Acute bacterial prostatitis is a suppurative prophylaxis characterized by fever, chills, leucocytosis and acute perineal and low-back pain. In more severe cases, there may be bacteremia, shock and DIC. Blood cultures are often positive with the same microorganism found in the urine.

"In the majority of cases, Escherichia coli, Proteus mirabilis and Enterococcus faecalis are the causative pathogens."

Staph aureus may also be found in cases that are associated with catheter usage.

[Slide.]

Chronic bacterial prostatitis may be asymptomatic or characterized by a sensation of perineal fullness, low-back pain, dysuria and pyuria. Fever is less common. It may be present. It may be low grade. The same microorganism is usually present with each recurrent episode. It is very difficult to eradicate because of the presence of prostatic calculi which serve as a nidus of infection.

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The microorganisms may be the same as the pathogens that are found in complicated urinary-tract infections or acute disease. Dr. Kunin's statement that "Coagulase-negative staphylococci, alpha-hemolytic streptococci and diptheroids are part of the normal flora of the male urethra and only rarely cause infections," is correct, of course.

However coagulase-negative staphylococci may be considered pathogens in certain patients with chronic recurrent disease. In order for them to be a pathogen, usually, they would have to be the sole organism and they would have to meet the other criteria for pathogenicity.

[Slide.]

Generally, submissions for this indication have provided for subjects with the chronic form of the disease as opposed to the acute. This is because of the difficulty in obtaining the appropriate bacterial specimens in patients who suffer from true acute disease. In other words, there is a danger, a real danger, of causing bacteremia while performing prostatic massage in order to obtain secretions.

[Slide.]

Therefore, in order to differentiate between chronic and true acute disease, it is strongly recommended

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for labeling purposes documentation be provided with regards to the duration of the present episode and the duration of the disease.

[Slide.]

An evaluable patient should present within -5 to 0 days of starting the study drug with either a tender, tense prostate on rectal exam, which is what you would find in an acutely ill patient, or acute prostatitis, or a soft, tender prostate without nodules which would be more consistent with a patient with chronic prostatitis.

[Slide.]

And one or more of the symptoms from the following; disturbances of urination, frequency, urgency, dysuria, disturbances of urination that might be more characteristics of lower-tract obstructions such as hesitancy, decreased stream, urinary retention, perineal or low-back pain, fevers or chills.

[Slide.]

The bacteriologic assessment for inclusion should include a urine culture as performed by the technique described by Drs. Mears and Stamey which includes the following four specimens: the voided bladder 1 specimen, which is the initial 5 to 10 milliliters of the urine

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specimen; voided bladder 2, which is the clean-catch mid-stream urine specimen; the expressed prostatic secretion specimen, secretions expressed from the prostate by digital massage after the mid-stream urine specimen is collected; and the voided bladder 3 specimen, the first 5 to 10Êmilliliters of urine stream immediately after prostatic massage.

[Slide.]

The diagnosis of acute or chronic bacterial prostatitis is confirmed by one of the following criteria: the colony count of a pathogen in the voided bladder 3 specimen exceeds that in the voided bladder 1 or voided bladder 2 specimens by ten-fold; or the colony count of a pathogen in the expressed prostatic secretion specimen exceeds that in the voided bladder 1 or voided bladder 2 by ten-fold.

[Slide.]

In the face of a true, acute prostatitis, as I have already said, it is not clinically indicated to perform a prostatic massage. Therefore, the division will accept patients with a clinical picture consistent with acute disease including a tender prostate as determined by rectal exam and with a voided 2 specimen with greater than or equal

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to 10^5 colony-forming units per milliliter of an accepted pathogen.

[Slide.]

Excluded would be patients with known prostatic cancer, the presence of any other infection at the time of enrollment that might require treatment with an antimicrobial other than the study drug, patients who receive treatment with any systemic antimicrobial for 24Êhours or longer within seven days prior to entry into the study unless there is documented evidence of bacteriological and clinical failure.

[Slide.]

Unevaluable are those patients who received another antimicrobial for a disease unrelated to the prostate and which might have had some effect on the disease under study during therapy or the full study period. This does not apply to patients who receive an additional antimicrobial for the treatment of prostatitis who would be considered evaluable failures.

Additionally, unevaluable are those patients who were lost to follow up or do not have documentation of microbiologic outcome. Again, this does not apply to patients who were previously documented failures.

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[Slide.]

For evaluation visits, the first visit is the baseline visit which may be called free-therapy visit, screening visit or start-of-therapy visit or a combination of the above. This visit may take place at five days before to the day of the start of therapy.

It may coincide with randomized and start of therapy in an acutely ill population or it may be split into two visits, an initial pre-therapy screening visit followed by a visit up to five days later to start therapy which you would do in a more chronically ill population.

The rationale for delaying the start of therapy in patients with a chronic form of the disease is to provide the ability to the sponsors to maximize the evaluable population by first screening them by a physical exam and culture and subsequently randomizing and starting therapy.

The baseline visit should include a history, physical exam, vital signs, blood work, a confirmatory, sequential urine culture, compatibility with the inclusion-exclusion criteria, informed consent. In cases of chronic disease, diagnosis may be confirmed prior to randomization.

[Slide.]

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The on-therapy visit can take place within a range of three-to-ten days after the start of therapy. This is completely dependent, on some level, with how ill the patient. In an acutely ill patient, maybe one wants to see the patient earlier as opposed to later.

This visit may be substituted by telephone contact and it is not necessary for evaluability. It should include a clinical assessment of the symptoms of prostatitis; in other words, a sequential urine culture and a rectal exam are not necessary.

[Slide.]

The FDA test-of-cure visit is at five-to-nine days after the end of therapy and should include an evaluation of clinical and bacteriological efficacy. In other words, a rectal exam should be performed, a quantitative bacteriological culture should also be performed.

If an expressed prostatic secretion--if material cannot be obtained after massage, then bacteriological efficacy may be based on urine cultures, the VB1, VB2 and VB3; in other words, all three specimens.

[Slide.]

There is the final visit which should take place four to six weeks after the end of therapy which we have

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called the end-of-study visit. This visit is utilized solely to assess for recurrence in those subjects who were cured at the previous visit. Efficacy evaluation should again include a digital examination of the prostate, clinical assessment and quantitative sequential urine cultures.

[Slide.]

An important aspect in the evaluation of prostatitis is the ability to quantitate symptoms and some type of symptom scoring system which, at present, does not appear to exist, or at least a validated scoring system. There are at least four questionnaires that I found in a search of the literature that potentially could be used. This is an issue that, certainly, needs to be looked at.

[Slide.]

So prostatitis evaluability should include both a clinical and microbiological assessment at the five-to-nine day post-therapy visit of the test-of-cure visit.

[Slide.]

The types of clinical outcome at the test-of-cure visit: cure, the complete or significant resolution of all pre-therapy signs and symptoms and failure, no response to therapy or worsening of most or all pre-therapy signs and

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symptoms.

Once again, the category of improvement has been omitted in order to provide for a dichotomous cure-fail analysis and any subject considered a failure at a previous visit or a previous time should be carried forward.

[Slide.]

Microbiological outcome at the five-to-nine day post-therapy visit includes eradication, a sequential culture obtained within the five-to-nine day post-therapy window that reveals that the pathogen isolated at entry has been eradicated from either the voided bladder 3 specimen or the express prostatic secretion specimen or both.

Persistence, a sequential culture obtained on or before the five-to-nine day after completion of therapy visit that reveals continued growth of the original pathogen in the expressed prostatic secretion of voided bladder 3 specimen.

[Slide.]

Superinfection, the isolation of a pathogen other than the baseline pathogen in an on-therapy specimen associated with worsening or emergence of clinical evidence of infection.

[Slide.]

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The four to six week post-therapy visit; again, to be considered evaluable for this visit, a patient should have been considered a cure at the five-to-nine day post-therapy or test-of-cure visit. Once again, all previous failures should be carried forward as failures.

[Slide.]

Clinical outcomes include sustained cure, all or most pre-therapy signs and symptoms remain resolved at the four to six week post-therapy visit and subjects classified as cures at the five-to-nine day post-therapy visit.

Failure, all patients who were carried forward as failures and relapse, the signs and symptoms absent at the five-to-nine day post-therapy visit that reappear at the four to six week post-therapy visit.

[Slide.]

Microbiologic outcomes include sustained eradication, a sustained eradication, a sequential culture obtained within the four to six week post-therapy window that reveals that the pathogen found at entry remains eradicated in the VB3 or expressed prostatic secretion specimens.

Persistence is the same definition as before. These are, again, carried forward. And recurrence, the

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isolation of the original pathogen at any time in the expressed prostatic secretion or voided bladder 3 specimens after the documented eradication of this organism at the five-to-nine day post-therapy or test-of-cure visit.

[Slide.]

So the FDA proposal that is being submitted for discussion is to study acute versus chronic disease or the separation of them in the document in order to provide for accurate labeling of the populations under study.

At this point, I d like the ask for questions and turn it over.

DR. CRAIG: Any questions?

DR. HENRY: I am afraid I need to ask for clarification. As a pediatrician, I don't see prostatitis so there may be things that are apparent to people who see this much more frequently. Actually, there were three things that I required some clarification. When you talk about the time when therapy would start, you say -5 days to 0. I assume that is primarily with the chronic. But why that window of five days? Is it really something that is necessary?

Bill, I can ask all three questions and you can go back or we can go one by one. So that is the first thing;

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why -5 days to 0? The second thing is with the expressed prostatic secretion culture, why do that when it seems like, when you talk about it later, it is almost the equivalence of the VB3. So can you simply eliminate the EPS culture?

Lastly, when you talk about cure, you talk about significant resolution. To me, that is pretty biased by the investigator and maybe that might create more problems than taking it out and having something more concrete.

DR. ALIVISATOS: To address your last comment, you're right; it is bias. That is why a symptom scoring system and the use of it would be very helpful because, up until now, what we see does not have something in that. It is just however somebody sees it.

We don't have the category of improvement anymore. So you have to be able to call a patient something and possibly a scoring system would be very helpful.

The wide range of days, -5 to 0, is only because of ease. You might see somebody on Thursday in the clinic and they might not be able to come back until Monday or there might not be a result. Otherwise, it certainly is a long period of time and something that you wouldn't do in acute disease.

EPS; the idea is to have expressed prostatic

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secretion cultures, and they are better than the voided bladder 3 specimen. I can't answer your question beyond that. I don't know, not being a urologist.

DR. MURRAY: One little question. You may have said this and I missed it. Eradication is defined as in the UTI?

DR. CRAIG: I will get to into that, because that is a problem. It is not defined. It means no bacteria, but it is based on what your sensitivity of the test is. It has been based, primarily, as I understand, on 10^3. So eradication is not well defined like it is in urinary-tract infections by saying exactly what it is, what your sensitivity is, which is what I think they need to do.

DR. ALIVISATOS: Although, up until now, when we evaluate these cultures and in previous approvals, there have been no bacteria. The original bacteria has not been present in those specimens, and that was eradication. None of it is there.

DR. CRAIG: But, again, it is less than 10^3.

DR. ALTAIE: Dr. Craig, we could outlie what method of quantitation to be used. Otherwise, we can indicate--use a larger sample, 0.01 or even 1.0, depending on how far down we want to go in sensitivity. And that is

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something easy to do. Once a quantitative culture is requested, you can switch your loop up or down. It is not a big deal.

DR. CRAIG: Are there any other questions or clarifications because I am the one that is to give the comments?

Committee Presentation

DR. CRAIG: I agree with the need to divide this into acute and chronic. I think the NIH consensus panel obviously felt that they were two entities. I think also there is evidence suggested that the duration of therapy would be different for the two, longer for chronic, shorter for acute prostatitis.

So I think it is appropriate to do it. I can't disagree with the definitions. They were made by Dr. Kunin who was my mentor, and who am I to question my mentor. So I think the definitions are fine.

I remember one case--he used to have a weekly session with the medical students. One came up and told him about this case of prostatitis they had downstairs. The student actually hadn't done the rectal exam because the staff, the residents, had told him that the patient was quite tender and not do to it.

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But Dr. Kunin went over this test, the Stamey Mears method, spelling out exactly what the student needed to do. So the student went down afterwards, did the rectal exam, and, several hours later that night, the patient went into Gram-negative sepsis because what he had was acute prostatitis, not chronic prostatitis.

So Dr. Kunin always included that or remembered to put that when he talked about that in his book. So I do think that they are different etiologies and, as I say, I think it is appropriate to break them apart. I am sure that your studies, though, are going to be primary chronic.

In chronic, there is no rush to start therapy before you know what you are dealing with. That is why one has the zero-to-five-day period there, to account for doing the test, finding out if you do meet the criteria that was put forth there where the number of organisms present in the prostatic secretion or in the urine immediately after massage are at least ten-fold higher than what one found in the first specimen which is just a culture of the urethra, in essence, and the second culture, the mid-stream, which is the culture of the urine.

So I think the zero-to-five days is appropriate. She mentions it allows the patient that has the test done on

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Thursday where they may not get the results back on Friday to come back and be entered in the study on Monday. So I have no trouble with that.

The inclusion criteria, I think, are okay. The one thing, though, that I thought needed to be changed a little bit is that when you are talking about the symptoms of obstruction that it be clear that those are new symptoms or worsening symptoms because, obviously, there are going to be elderly patients who will have a background of hesitancy and some decreased stream.

I think you would want to, if it is going to be one of the symptoms that is going to be used for using that as a criteria, I think it needs to be that it is either new onset or worsening symptoms of obstruction that have been associated with the infection.

In terms of the diagnosis being primarily based on the tender exam and these symptoms but, also, on the microbiologic definitions, I think you need to be a little bit more specific. I have no trouble with using 10^3 as your cutoff so that what you are talking about with prostatitis is having somewhere around 10^4 organisms or higher.

If one went down lower, so that you were looking at 10^2 in urine and your first specimen, then you could go

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up to 10^3. But, again, when you start getting down to those very low numbers, I worry more about problems that can happen in the laboratory with contamination.

So I would prefer it staying up at the higher numbers using 10^3 as your sensitivity lower limit so that, in essence, you are implying that there is going to be 10^4 bacteria or more in your prostatic secretion or in the urine obtained.

I think it just is going to increase the specificity that what you are really dealing with is truly a prostatitis. But I think that needs to be spelled out a little bit more in the thing.

The same thing when it comes to eradication. When one is looking at the outcome, one, again, needs to specify exactly what the degree of sensitivity of your assay is so that, again, I think you can be more specific just like you have been more specific for urinary-tract infections exactly as to what the definition of eradication means.

It is listed in here, but all it says is that the organism is eradicated. But I think it needs a little bit more.

Furthermore, although you did have on the slide that you talked about clinical success being complete

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elimination of signs and symptoms or significant disappearance of them, what is actually in the written document in the blue book is resolution of all signs and symptoms for clinical cure. Clinical failure is no response to therapy.

I think you are going to have patients that clearly fall in between so I think you need to decide, if you want your improvements to be actually under the clinical failure, you are going to have to reword that a little bit so that the clinical failure might say something to the effect of incomplete resolution of signs and symptoms as well as no response to therapy because you will find some people that may have some slight improvement but, if one was using a scoring system, it might not be a major difference that one gets out of the score.

I support the use of trying to get a scoring system and I would suggest that people try a variety of ones so that, with time, you might be able to, with those scoring systems, then, be able to decide on something that does validate reasonably well for clinical cure and that, then, you can be more specific in later times.

As you listed it right now, I think you encourage people to use one of the scoring systems and I would agree

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with that use, and I agree right now, I couldn't pick which one. If you talk to the various urologists, you would get their bias, not necessarily a good answer as to which one is the best for actually doing the studies.

Lastly, coming again with some of the things that we mentioned. We were talking about urinary-tract infections. Some of the same names are here. If we are going to call the clinical relapse "recurrence," then the same thing needs to be done in prostatitis.

You have got the thing there called relapse, again, where it should be, as I say, recurrence if we are to keep consistency. If one is going to make those changes for UTI, one needs to make the same changes here.

Similarly, when one is talking about the microbiologic outcome in terms of superinfection, recurrence, persistence, one needs to make the same sort of comments that were made before based on the fact that, for most situations, we can't really be sure that it is not a new organism unless it is a different species, genus and species.

So those would be the comments that I would have. But, overall, I think you did a good job of sort of pulling together what was there from the previous guidelines and

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what the IDSA had sort of put together and coming up with a reasonable design for doing these trials.

But, again, I think they can always be improved and, clearly, since clinical outcome is an important aspect of it, trying to have use of scoring systems and evaluate those, I think, would be very useful in these trials.

Committee Discussion

DR. CRAIG: So, other comments, questions of me or the FDA? Silence?

DR. MURPHY: Off the clinical part and on to the analysis. Dr. Wittes, did you have any comments about the fact that we really have this document dealing with the same issues as you brought up before?

DR. CRAIG: I would think you would with the evaluability, the ones that you are calling nonevaluable that are the same criteria, that you would have to do both an intent-to-treat as well as looking at your evaluable patients.

DR. WITTES: That is what I would say, just make sure that the sample size is adequate for that intent-to-treat analysis.

DR. MURPHY: Thank you.

DR. RELLER: In the dichotomous assessment for

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cure-failure, would it be helpful to define the cure as complete resolution of symptoms or nearly complete such that no--something in there that no further therapy is sought, because I think that complete resolution of symptoms in these patients with chronic prostatitis is what everyone would like to see but it may be that, over time, one redefines what one is willing to live with.

I think that it is not good enough the way it is, but to put some parameters around it, either that it is complete and that is what you want for a clinical cure--but, to me, one of the issues is whether or not people no longer seek or are prescribed or given any further therapy, that it is sufficiently good to not go any further with the entity.

DR. CRAIG: With the way that the study is designed, you would be able to have that out for four to six weeks, whether they went back on another antibiotic. Although your are looking at five-to-nine days, you are also looking at four to six weeks after completing therapy to look and see if the initial improvement has continued or whether there is a recurrence instead of a relapse of clinical symptoms.

So that is as far as it is currently being--the recommendations are to follow it out. Are you suggesting

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that it should even be longer?

DR. RELLER: I have no problem with making it complete. I think that it either has to be complete or there have to be some boundaries around anything that deviates from that, but it can't be ambiguous because this is an exceedingly ambiguous--the reality is it is an ambiguous endpoint.

So if you want complete, then I think we have to readjust what are going to be acceptable or expected complete cure rates, is what I am trying to say, which I think is fine. It eliminates the ambiguity. But it is too fuzzy not to have it either complete or anything less than that that is objectively defined as what one is going to accept, even if it includes a longer follow-up period.

DR. CRAIG: If one has a scoring system and one can probably look at several of those scoring systems, one could at least, from a scoring system, have what you would require in terms of a point drop or something like that in order for that to occur.

DR. RELLER: But I am thinking in terms of what to do now until such a thing is validated so that, perhaps, the thing to do would be to have complete resolution of symptoms out to the time period of follow up now and then the failure

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is no response or incomplete resolution of symptoms and that if one, then, has grading systems evaluated, that one could subcategorize those patients over time and later that the definition of cure would be modified to say complete resolution of symptoms or reduction in X score of so many points, or whatever, for the future, but to come to some resolution, consensus, now as to what the document would say.

I, personally, would favor complete resolution of symptoms until a scoring system is validated that would enable one to redefine cure.

DR. CRAIG: I think that is what the intention of the agency was is to make what was so-called improvement, before, under failure instead of having it, necessarily, be success. So I think what needs to be modified, what I see here, right now, is your definition of failure. Right now, failure essentially says no response whatsoever.

People may have a slight response, where they might have been called improvement in the past, but didn't have complete resolution of signs and symptoms, and those are the ones that you are looking at in terms of trying to reclassify them.

So that is the definition that needs to be revised

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to pull in those that also may not have complete resolution.

DR. MURPHY: Being a pediatrician, I am also going to plead ignorance. What I am hearing you saying, if we look at that slide that says cure--

DR. CRAIG: The slide is different than what is in the text. So the text adds the word "significant."

DR. MURPHY: So does the slide.

DR. CRAIG: I mean the text does not have the word "significant."

DR. MURPHY: That is what I want to get at. You are saying cure should be complete resolution of all pre-therapy signs and symptoms and then failure should be not compete.

DR. CRAIG: It is one of those things, is all signs and symptoms entirely going to go away? These are elderly people, especially if they already have some hesitancy, have some decreased stream.

DR. MURPHY: With defined baseline. I guess you would have to have defined baseline.

DR. CRAIG: Return to baseline is what you are looking for more so than complete resolution because--

DR. MURPHY: Complete or return to baseline?

DR. CRAIG: I think you need to put that in there

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because I don't think you are going to find everything going away. These are not necessarily going to shrink the prostate and do all those kinds of things as well, or they would be used by all males.

DR. MURPHY: Thank you.

DR. RELLER: The definition of failure would be no response or incomplete resolution of symptoms, failure to return to baseline, some wording along those lines.

The second thing that I wanted to strongly encourage, to avoid confusion, is that the terminology, because you are looking at microbiological endpoints, be consonant with the descriptive terms, recurrence be consonant with the urinary-tract-infection document.

Thirdly, to put specifics for the laboratory that wrestle with these specimens, including expressed prostatic secretions as well as, in some patients, the VD3 versus the earlier samples.

I think most people believe that the specimens actually received often are of lower colony counts than in the flagrant urinary-tract infections. So I would favor 10^4 or greater, but that it would be put in there as a documentation for the pathogens present which will be uropathogens, primarily.

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Similarly, one would logically, to be consistent, in terms of the reduction of biomass that Dr. Sheldon aptly described, then it would be less then 10^3. But to enable one to delineate accurately those persons who persist with the same genus and species, it would be nice--you could have 10^3 or more, then, would be the persisters.

Consequently, one could have technically a single colony so that it would be advantageous to recommend, and it doesn't cost any more and laboratories are used to doing this, to have the follow-up specimens cultured with the hundredth-of-an-ml loop that would give you the same assurity and the reproducibility of counting the numbers.

Basically, one would be shifting one log down, everything, including the definitions, the endpoints, et cetera, for urinary-tract infections and the microbiology of acute and chronic prostatitis. I think it would make everything a lot more logical and make it easier for the microbiology part of the agency to deal with this.

It would not cost any more. You don't have to use different media, et cetera, but it would enable one to have greater certainty about whether the organism that is there is the same or not and whether it is really gone, if that turns out to be the case.

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Dr. Altaie, what do you think?

DR. ALTAIE: To add to your comments and to agree with them, I would say yes, you need to bump up the sample to 0.01, and you also have not a problem with the contamination because the population is pure male population. So you don't have those limitations with the techniques.

It is probably appropriate and I have no problem with it.

DR. CHIKAMI: Just a point of clarification. Were you suggesting that for both the diagnostic culture and the follow-up culture that a 10 microliter would be used?

DR. RELLER: You could do it that way. It would just mean that a positive, instead of being ten colonies, would be 100 colonies. It doesn't change the numbers at all. And laboratories are used to having both kinds of loops available. You could do it either way. It is just that, for the test-of-cure, the follow-up cultures, one would be using a hundredth of an ml, 0.01 loop for those.

DR. MURPHY: I guess, Barth, the question is would there be a problem in actual pragmatic implementation in samples if you are using one size loop for one specimen and another size loop. You would have to set it up so that the

lab would be totally keyed into this issue if you do that.

Do you see what we were saying?

DR. RELLER: I think it is fine for these study patients to use a hundredth of an ml loop. You keep the same numerical definitions but it gives you the same precision with both the complicated urinary-tract infections in dealing with prostatitis. The differences and the accuracy of measurement of the biomass reduction and all of those things, it just hangs together more tightly and enables you to have consistency.

DR. MURPHY: We are agreeing. I am just addressing the pragmatics of do you think that will be a problem or do you think it we be better to go with one loop size.

DR. RELLER: I think it would be simplest to use the same loop for all specimens in these patient studied with acute and chronic prostatitis. That would simplify matters. It is not a problem. You could delineate that.

DR. CRAIG: If you were using a hundredth, to a 10^2, as your cutoff, I could even see going down a little bit to five times 10^3 for my cutoff as well and not necessarily being at 10^4. I am not sure that five time 10^3 is going to be much different from one times 10^4 in terms of

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bacterial numbers.

But it is a significant difference if you have got only and 10^3 cutoff. You are not sure, then, that your prostatic secretion is going to be tenfold higher than what your other organisms are.

DR. ALTAIE: And that would be a limitation to the technique in the way we do the studies. So I would suggest a 0.01 to be used, or 10 microliters to used, for both entering and exiting the study and the limits remain the same, but we would have more accuracy with the larger sample.

DR. LEISSA: Brad Leissa, FDA. I just want to make two comments. One had to do with the issue--this is about the clinical assessment at test-of-cure. One is a general comment to the issue of improvement. The improvement category, as Dr. Albrecht mentioned earlier, was often a contentious issue when it came to looking at the data as it came in because some improvement are not sufficient.

You would see a patient classified as an improvement yet what you would then see would be in the concomitant therapies a patient being placed on a new antimicrobial for the indication,

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Another patient had everything but one or two signs or symptoms and, therefore, not a complete resolution. But, sure enough, they didn't need any other therapy. So just to add some context to the discussion of improvement.

But also I guess I would throw into the issue of ambiguity for this indication, at least, is because we are studying together acute and chronic prostatitis whether or not different definitions are needed for the same, so that for acute prostatitis, getting "significant improvement" may not be enough for that versus, in chronic, yes, getting back to baseline is important.

DR. CRAIG: You are probably right. I would say for acute, you would probably want to go all the way back, all signs and symptoms.

DR. LEROY: Bruno Leroy, HMR. I would like to come back to the categorization improvement and failure. Don't you think that, in clinical practice, what you call a failure is when you need to prescribe a new antibiotic, in fact, and do you expect that the investigator could call a failure something from which they do not prescribe any antibiotic?

This will create a problem because they will probably say that the symptoms have disappeared whereas they

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have not disappeared. They just don't want to call it a failure. I think that the cutoff really is the prescription of the new antibiotic.

In fact, there is a need to have this category, improvement, significant improvement, significant resolution of the symptoms with no antibiotic prescribed. This is the exact cutoff that you can obtain.

The problem, when you ask an investigator to say that patient is a failure, whereas he has just stigmata, post-infectious stigmata, you will have a problem. You will just say this patient has no more symptoms.

DR. CRAIG: So we would have that out, at least for four to six weeks, that they have been off an antibiotic.

DR. LEROY: I do think that the cutoff is really the prescription of a new antibiotic. In fact, in some of the documents--

DR. CRAIG: Yes; that is clearly in here that starting on another antibiotic is considered a failure.

DR. ALBRECHT: Right. I think the points you raise about the use of a concomitant antibiotic, that is fairly clear. If you use it, it is a failure. If you don't, it is not. You raise the issue of post-infectious

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stigmata. I think sometimes when something is a non-infectious--well, it is a sequela of the infection but not a symptom of the presenting disease.

We actually have made specific comments about that, for example, in skin and skin-structure infections where we recognize that the discoloration after an infection should not be interpreted as the erythema or edema of infection.

So, in those scenarios, we do try to--I think this was an attempt, as Dr. Leissa has pointed out, to try to prevent this, "at all costs, I want to have a very optimistic viewpoint and I am going to push everything up to a high success rate," and, instead, what we are trying to do is recognize what was the role of the antimicrobial in effecting a difference in the patient's course.

I think we believe, and this actually was recognized in the IDSA guidelines of 1992 where the recommendation under clinical response is made as follows: the clinical response should be designated as cure, failure or indeterminate outcome, that third one.

But it is asking for a dichotomous, is it cure or is it a failure. I think we want to be fairly strict about the term "cure." I recognize your objection to the term

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"failure," and that is why sometimes we have said cure/not-cure. That option certainly exists, but I think it is, as Dr. Craig alluded to earlier, an attempt to say this antimicrobial effected a difference.

With chronic diseases, we recognize the problem of you don't cure all the signs and symptoms because there are the baseline ones. I believe, under acute exacerbation of chronic bronchitis, we actually are very specific in saying that the expectation under clinical cure is--let me read it here; "For patients with chronic bronchitis, this should be interpreted as return-to-baseline conditions."

So we recognize that everything won't go away, especially a patient presented with that. But there is an expectation, and we are trying to use the word "cure" to mean a return to what the patient started with before the acute onset. It is strict.

DR. LEROY: But I think that the investigator will probably go to say that there are no more symptoms whereas there is a simple minor symptom. The cutoff for him is, "Since these symptoms are minor, I do not prescribe, so that is not a failure for me. That is a cure." That is the problem we will face.

DR. ALBRECHT: I think that goes to the issue that

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has been raised in the context of this indication and others that if we had some symptom scores that we could use, and we would all agree that if a patient presented with a symptom score, whatever its numeric value, and it went to a 0, 1, 2 or something along those lines, that we would agree that a minor something does not constitute a non-cure.

DR. CRAIG: I agree. That is the reason why I would also support using a scoring system so that one can help the agency make a decision on those few patients where there may be one little symptom that might not fit the definition but if you have a scoring system that shows there is a marked change in the score over time might make them feel very comfortable in calling that a cure.

DR. ALBRECHT: Let me make a comment on symptom-scoring systems. We did not feel, from the agency, that we should be responsible for saying this is the symptom score we would like you to use for all your studies. But rather, what I would like to say is I would like to invite industry actually, in context of the actual studies, to propose what scoring system they would like to use because, again, we can't be seen as endorsing something unless it has been so validated that it becomes the standard across the board.

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I think we look to our advisory committee and to industry to help us make those kinds of recommendations.

DR. LEROY: The problem of the scoring system is the cutoff when you apply cure or failure. That is the problem of the scoring system because, to record the score, is something but then to apply categorization based on the cutoff, it is impossible if the score has not been validated and the cutoff has not been validated.

DR. ALBRECHT: Right. And I think, also, we need to recognize sort of the sequelae of that. This was pointed out by Dr. Soper yesterday when he said if you start to look at these things strictly, just recognize that the cure rates you are going to be reporting are going to be lower than what we said before.

I think, as I mentioned in my promotion balance-slide, we are seeing that and we do recognize that. I think it is, again, just an attempt to very openly say yes, these are the definitions we are using and the implications of that are that the cure rates, which do reflect essentially complete resolution, are lower than what we used to call success rates where it was a patient got a little better or substantially better or completely better.

DR. LEROY: Thank you.

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DR. HOLLEY: Preston Holley, Glaxo Wellcome. I had similar comments. I think the biggest issue seems to be the test-of-cure at the five-to-nine day visit because a lot of these patients, as was mentioned, may not be totally resolved at that point but may not need further antibiotic therapy, particularly in the patients with chronic prostatitis who have chronic symptoms of prostatic hypertrophy, many of those with the same symptoms that are being asked to be recorded here that would be recorded on a scoring system.

So if a patient, for example, came in with chronic prostatitis and you are using a scoring system and they had a total score of maybe 12 or 15 based on these symptoms, and it went down to 3 or 4 but those were the baseline symptoms, you don't have the baseline on that patient. You never got the baseline scoring on that patient.

So I think there is going to be some ambiguity and difficulty in trying to determine what is baseline by the physician that is actually scoring this. If you are calling that patient a failure at the five-to-nine day test-of-cure visit, there may not be any follow up on the failures for long-term.

So I would suggest that you at least consider a

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possible category of improvement at that visit for patients to continue on to the four to six week follow up where, at that point, if there have been no further antibiotics or anything and all those symptoms are resolved, that that could be considered a cure at that time, or something along those lines.

DR. ALBRECHT: The issue you raise of the difficulty of knowing the baseline is one I think that crosses a lot of indications. Dr. Rakowsky actually pointed that out yesterday in his discussion of meningitis where he said, "You may not get it right as you are seeing the child in the emergency room, but, in the next few days, do try to establish their baseline."

We recognize it is difficult but to try to assess whether the patient's acute disease got better, we need to have something to compare it against. In some acute infections where the baseline was a perfectly healthy person and, when they resolve, they become, again, a perfectly healthy person, it is kind of easy and we say complete resolution of signs and symptoms.

When we have got underlying diseases or conditions, that becomes very difficult and, again, I think our hesitation in including improvement is simply because it

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is such a nebulous area and it has been interpreted in so many different ways.

Again, I guess maybe if I could just repeat, even if we say whatever the symptom score everyone proposes, that we will all agree that a score of, whether it is 75 percent reduction or going down to less than whatever value, we could all agree to use those terms.

But I think, historically, what we have seen is the term "improvement" meant something different to everybody and it was very difficult, then, to try to make sort of across-results comparisons or assessments of whether on drug's improvement was the same as another.

DR. CRAIG: But I think he does present a valid thing in looking at scoring systems where, as you say, the baseline may be the best you can get to. So it may be that you can't go back all the way to normal and that the score is going to be somewhat higher than what would occur in acute prostatitis where essentially you started with somebody that had no prior symptoms and essentially got an acute episode.

So it does make interpretation of the scoring system somewhat problematic but I still think the use of a scoring system gives you a little bit more quantitation in

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terms of the symptoms and can be helpful for trying to decide on the clinical outcome in a disease that is very difficult to evaluate.

DR. HOLLEY: I would just like to comment again and say that I agree with you, Dr. Craig, on that point. The real issue is whether or not further antibiotic therapy is necessary. That is why I am saying that if there could be a little more flexibility rather than total resolution of symptoms at that test-of-cure visit that, then, you could follow that patient on out to the follow-up visit and, if there were no further antibiotic therapy required, and the patient was returned to baseline, then that, to me, would be a cure.

Thank you.

DR. MURRAY: I think I agree with that point, too, in some concepts. It is kind of like the cellulitis where you have still got some abnormalities of the skin that continue to resolve over time. I like that idea.

DR. ALBRECHT: Let me ask a practical question in context of that because what we often will see in these clinical studies is the patient who is seen a baseline is seen at the five-to-nine, this comment about improvement is made, and then the patient is lost to follow up.

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I think we have wrestled with, "And then what do we do?" We actually have recommended the later follow ups on a variety of infections to determine what is going on with the patient that looked like they were getting better but we don't know--

DR. CRAIG: But I think if you didn't have the later follow up, that they couldn't provide that, then you would have to assume that it was a failure.

DR. MURPHY: Correct. The implications of that need to be followed through. Then that patient becomes a failure.

DR. CRAIG: In some regards, that may be good so that we get a longer follow up on some of these patients.

DR. WITTES: The incentive to follow up.

DR. ALBRECHT: Our definition of failure at five-to-nine days is "not cured." We kind of cover for that and, if we do have that later date as showing that everything went well, we can argue to reassess that the patient, in fact, should not be classified a failure.

DR. COCHETTO: David Cochetto from Glaxo Wellcome. Those of us males at Glaxo Wellcome have a particular interest in this topic. But, beyond that, as far as developing instruments further, we are interested in that,

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obviously. I wonder if, on the industry side, we don't get hung up sometimes on what seems like a daunting task because of the word "validation."

Maybe the committee can help us with that, and FDA as well. If, instead of thinking in terms of validating symptom-score instruments, can you give us some insight into what information could be presented with clinical trials that would convince you that symptom-scoring instruments are providing clinically useful, clinically meaningful, indices of change.

DR. CRAIG: Again, I think what someone mentioned earlier, the fact that further antibiotics were not required in patients that got down to a certain score would be one of the things that would let one feel that getting down to a certain score was a cure and did not result in further antibiotic therapy.

Correlating, also, microbiologic with response with what one sees in terms of the score, too, where, if there is persistence, the score does not change as much and stays relatively high while, in the situation where there is elimination, eradication, of the organism, one does see the score going down.

Those are the kinds of things that you would like

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to see, at least in my mind, to make one feel that the scoring system is explaining the disease process.

I don't know if anybody else has other comments.

DR. WITTES: I would like to say something. I second, very strongly, what you have said. There is a lot of literature about validation where much of the validation is sort of internal validation of concordance of one variable with another.

But it seems to me that it is exactly the concordance of the clinical change and that one wants to look at the way in which--not only the way in which the scale correlates with status but the way the change in scale correlates with change in clinical condition.

DR. CRAIG: The way most of these things are devised is looking at your experience that you have had with a bunch of patients that you have documented in all this data, and then sort of finding things that sort of correlate with the response.

That's fine for the dataset that you have looked at retrospectively but what needs to also be done is, in a prospective way, to see if it also is predictive of what one is going to see when it is used in a prospective way, not just looking at it retrospective on an initial collection of

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patients.

Those are the things, I think, we mean when validated. Some of the things that they have done in pneumonia that Mike Fine out of Pittsburgh has done, trying to look at prognostic factors that would predict outcome in pneumonia. He has developed those and then he has taken those factors, looked at them prospectively at other centers and has been able to validate the scoring system that has been used.

So those are the things, I think, we need to have done so that there needs to just be more prospective use of it in clinical trials.

DR. RELLER: To amplify and, perhaps, be a little more specific on the comments that Dr. Holley made that I agree with, particularly with chronic prostatitis, that if one had patients who were clinical failures, when they come back and five-to-nine days, complete resolution of symptoms, success. No response or incomplete would be considered failures.

But the sponsor would be able to categorize as cures those person who had complete resolution of symptoms if they came back and four to six weeks and persisted in having less than 10^3 organisms on their microbiological

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examination.

It would be an incentive, and actually what may be a fairly frequent occurrence, is five-to-nine days, no organisms with the successful therapy--I mean, with good therapy; organisms, incomplete resolution of symptoms, clinical failure at that time. But, if you follow them long enough, in fact, they do get better.

Those patients who still had organisms are unlikely not to have them based on the natural history of the disease. So having a delineation as to no response or incomplete at five-to-nine days and the capacity to make them cures out at four to six weeks would be, it seems to me, helpful and an incentive to get the follow up and accommodate the natural-history considerations that Dr. Holley properly pointed out.

DR. CRAIG: Obviously, wording would have to be changed because the way, right now, that you have failures are carried through as failures all the way through.

DR. MURPHY: It sounds like a suggestion we will definitely consider.

DR. CRAIG: Any other comments?

It's break time.

[Recess.]

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DR. CRAIG: Our next topic is on streptococcal pharyngitis and tonsillitis. The FDA presentation will be done by Dr. Makhene.

Streptococcal Pharyngitis and Tonsillitis

FDA Presentation

DR. MAKHENE: Good morning.

[Slide.]

I will be presenting the indication of streptococcal pharyngitis and tonsillitis. Originally, this presentation was to have been given by Dr. Nasim Moledina, but she is unable to do the presentation. I will be doing the presentation in her place.

[Slide.]

This clinical entity that is being addressed in this guidance document is pharyngitis as a result of Strep pyogenes. The indication deals specifically with Strep pyogenes because this is the most important pathogen of the bacterial and viral pathogens that are associated with pharyngitis.

Clearly, there are other bacteria that will cause acute pharyngitis and, in particular, there are other streptococci that are associated with pharyngitis and tonsillitis, specifically group CNG. But these are rarely

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associated with sequelae and so are not covered under this indication. As I said, the indication does not, also, cover viral pharyngitis.

[Slide.]

For study considerations with this indication, one statistically adequately and well-controlled multicenter trial is what is suggested. In addition, adequate microbiologic data and PK/PD data should be provided to support the claim of clinical effectiveness.

For the PK/PD data, what should be included is tissue distribution studies to demonstrate that there is diffusion of the agent under consideration into tonsillar tissues.

[Slide.]

Further study considerations; although microbiologic eradication is the primary outcome parameter for the indication, it is important that the study establish correlation between clinical cure and bacterial eradication.

The last of the points is that any product with an absolute eradication rate of less than 85 percent ordinarily would not be approved as first-line therapy for pharyngitis.

[Slide.]

Streptococcal pharyngitis is an infection that is

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commonly seen in school-age children between the ages of about five and eleven. However, all age groups are susceptible for the infection and, that being the case, male and female patients of any age may be enrolled in these clinical trials.

For inclusion, patients should have a clinical diagnosis of acute strep pharyngitis with a history consistent with the acute presentation and, in addition, clinical presentation based on physician exam.

Patients with scarlet fever may be enrolled in these trials because, other than rash, the epidemiologic clinical presentation and sequelae of scarlet fever are no different from those that are seen with just acute strep pharyngitis alone.

[Slide.]

As far as clinical features when considering inclusion criteria, there are clinical features which are consistent and probably predictive of what you see in patients with acute strep pharyngitis although they are certainly not definitive. But they will give you a better idea of whether the patient is more likely to have an acute strep pharyngitis as opposed to another etiology.

These patients tend to have abrupt onset of sort

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throat which is accompanied by headache and fever at presentation. They may also have pain on swallowing. In addition, we look for erythema and exudate in the oropharyngeal area.

Additionally to note is that children will commonly have GI symptoms associated with their acute strep infection.

[Slide.]

Also to note is that, in general, patients will have tender and large anterior cervical nodes. Certain clinical features can help you exclude patients in whom a viral etiology is suspected and, most commonly, in these patients, symptoms are consistent with a ear or eye infection and, in these patients, unlike the classic presentation where they have abdominal pain and nausea and vomiting, diarrhea is a clinical feature which is more commonly associated with the viral etiology.

[Slide.]

In this slide, essentially what I would like to point out is that, as I have previously said, patients of all ages may be enrolled in the clinical trials. However, when enrolling patients of a very young age in the clinical trials, it is important to be aware that the presentation

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may not always be the classic presentation.

These patients tend to have the ear or eye symptoms of rhinitis or coryza and may have a more generalized adenopathy and a protracted course.

[Slide.]

As far a lab criteria, when considering inclusion of patients, it is important to obtain a specimen for culture from the posterior pharynx and/or tonsils if they are affected. Of course, it is expected that, from this baseline specimen, Streptococcus pyogenes would be isolated.

[Slide.]

What I would like to point out in this slide is that we are aware that rapid-antigen are available and there are probably many that are being used out there for screening. However, they are not as reliable as culture because of low or variable sensitivity.

That being the case, there are patients who are identified who may be false negative and actually do have an infection but do not get treated. For this particular infection, knowing that treatment of acute strep pharyngitis will prevent the nonsuppurative and also the suppurative sequelae of this infection, it is important to be able to identify those patients up front and not exclude them either

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in the trial or not exclude them for treatment in general.

So, having said that, if a rapid-antigen test is being used, the results should be confirmed by a culture that is obtained at baseline.

[Slide.]

As far as exclusion criteria, probably the most important has to do with chronic carriers. These patients, for the most part, are patients that have colonization with Strep pyogenes in the upper respiratory tract. They may also be identified as patients that have repeated culture-positive episodes typically with a mild presentation or atypical symptoms.

We need to be able to identify these patients in order to exclude them from enrollment because they can confound the results at the time of analysis of outcome.

[Slide.]

For the study drug to be evaluable, the patient should receive within 80 to 120 percent of the prescribed dose and/or dosing regimen of the drug. Any FDA-approved drug and dosing regimen is acceptable as the comparative agent.

[Slide.]

There are four visits which should be included in

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these clinical trials. The only thing I would like to say about the slide is that there is no end-of-therapy visit in this indication.

[Slide.]

At entry, patients should have documentation of an acute episode of strep pharyngitis; that is, essentially, the presentation should be consistent with what you would expect in acute strep pharyngitis, as I have previously mentioned. And, of course, a physical exam with emphasis on the ENT, the ear, nose, throat, exam. In addition, a throat culture for group A strep isolation and susceptibility testing.

[Slide.]

The next visit is the on-therapy visit. This visit is strongly recommended for a good study conduct because, essentially, at this visit, we would like to assess the early clinical response to therapy. This is the opportunity, essentially, to figure out if any of the patients are failing therapy and if so-identified, make the necessary adjustments in the therapy.

In addition, a clinical evaluation and throat culture may be done.

[Slide.]

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As mentioned, I think by Dr. Albrecht, this visit to facilitate patients being able to have this documentation, if they are not able to come in for a visit, this may be done via telephone contact and with specific questions and responses being noted in the patient record.

The visit, as outlined in the document, is consistent with the 1992 IDSA FDA guidelines.

[Slide.]

The third visit is the post-therapy visit. This is also the test-of-cure visit. This is the visit at which the assessment of outcome is made. This visit occurs approximately fourteen to eighteen days after the initiation of therapy. Of course, a clinical evaluation is done. The throat culture is repeated hopefully to document eradication of the organism and also, depending on the results, any susceptibility testing.

Again, the timing of this visit, as outlined in the document, is consistent with what is in the IDSA FDA guidelines.

[Slide.]

The last visit is the late post-therapy visit. This occurs approximately 38 to 45 days, or five to six weeks, out from the initiation of therapy. The purpose of

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this visit is to make assessments about relapse in terms of the infection and also make assessments about clinically whether there is any indication of the presence of the nonsuppurative sequelae that we are most concerned about with acute strep pharyngitis.

[Slide.]

The only other thing that I wanted to note specifically at the late post-therapy visit is that, in making these assessments of the presence or absence of the nonsuppurative sequelae, this is based, essentially, on the clinical presentation as there is no serologic documentation at this visit.

Again, the timing of the visit is what is consistent with the IDSA FDA guideline.

[Slide.]

As far as making an assessment of outcome, as I previously noted at the beginning of the talk, this is a microbiologically driven indication although it would be expected that in a patient in whom you document eradication of group A strep that there would also be resolution of clinical symptoms.

[Slide.]

The microbiologic outcome is defined in four ways.

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Documented eradication is the absence of the baseline pathogen at the test-of-cure visit. Persistence with this indication is the presence of the baseline pathogen as assessed at the test-of-cure visit.

[Slide.]

Recurrence occurs when the culture for group A strep, the throat culture is negative at test-of-cure visit but positive at the late post-therapy visit. Continued eradication is the documentation of negative culture both at the test-of-cure and the late post-therapy visits.

[Slide.]

Clinical outcome is defined in two ways; cure, which is the general definition that everyone is using; resolution of signs and symptoms at the test-of-cure visit and also that no other antimicrobial agents have been prescribed during the study period.

[Slide.]

Failure, essentially, includes those patients who have received at least 72 hours of therapy but may have persistence of signs and symptoms or the appearance of new signs and symptoms at the time of evaluation and also patients that may be given additional antimicrobial agents or their therapy is changed in some way.

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[Slide.]

There can be an assessment of clinical outcome at the late post-therapy visit. The emphasis here, again, is to make some comment or make some assessment of whether there has been any change in the signs and symptoms, essentially whether patients that were considered cure at test-of-cure visit continue to be cured or whether other new symptoms have emerged and, also, some comment or evaluation about the presence of post-strep sequelae.

[Slide.]

Specifically looking at the issue of bacteriologic outcome, there have been reports in the literature of late regarding bacteriologic failure rates. In a metaanalysis, the results of which were published in Pediatric Infectious Disease Journal in 1993, Mike Pichichero reviewed nineteen studies that were done between 1970 and 1990 and found that the bacteriologic failure rates varied or there was a statistically significant difference between penicillin and a variety of cephalosporins.

Again, as I mentioned, there are the reports that state that bacteriologic failure rates may be as high as 20 to 30 percent.

[Slide.]

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However, in the next year, in the same journal, Pediatric Infection Disease Journal, Stan Schulman and a group of colleagues published another study in which they had reviewed, actually, altogether 73 studies between 1953 and 1993, had grouped them by time periods and found that there was no significant difference in the bacteriologic treatment failure rates when looked at by the two eras.

[Slide.]

So, with that as a little bit of background, the issue that we would like to committee to address this morning is whether, with the reports of the high failure rates, is penicillin still an adequate comparative agent.

That is the end of the presentation. If anyone has any questions at this point, I can entertain those. Otherwise, Dr. Celia Christie will have some comments regarding this and other issues

DR. CRAIG: Any questions or clarifications?

DR. NORDEN: Just one question, and that is the question of the need for tissue-distribution studies for tonsillar tissue and levels. I have asked Bill. My impression is that most tissue-distribution studies don't add anything, that most drugs get into tissues well. I don't know what we are going to learn.

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DR. CRAIG: Obviously, what you are going to find with tonsils--with beta lactams, they don't go intracellular so when you grind up tissue, you are going to mix the intracellular fluid with the extracellular fluid and you are going to have, usually, concentrations that are less than what one sees in serum.

On the other hand, for drugs that go intracellular like macrolides, you grind it up, you are going to have higher concentrations. So I think it is fairly predictive ahead of time and I am unaware that it is really of much value for treating organisms that are primarily extracellular.

DR. NORDEN: Thank you. Therefore, I think we shouldn't require it.

DR. RODVOLD: In addition, if you are going to require them, I think you have got to put some guidelines in when to sample so that you don't get caught in hysteresis of tissue differences versus blood differences because you can line up the study so that--I can do the study so it is there but it doesn't really tell you how long it is going to be there and those types of things.

Then you get in the other argument that potentially is how long is being there adequate enough if

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there is anything to evaluate. Then you fall back to all the characteristics of the drugs. Different drugs have different situations of dynamics to them.

So the statement is too loaded, or too general. If it is going to stay, I think it has got to be a more specific guide.

DR. CRAIG: Dr. Reller, this is a clarification?

DR. RELLER: Yes. Dr. Makhene, the metaanalyses that you summarized, were there differences between penicillins and cephalosporins or was the issue addressed as to late sequelae, clinical response and eradication based on throat culture.

The basis for the comparison is what I am getting at.

DR. MAKHENE: So you are wondering whether there were--

DR. RELLER: The differences, the 10 percent no-difference and the 16 and 18 percent, was that for the three components, clinical presence or absence of the group A streptococcus and post-streptococci sequelae. Were there no differences for any of those criteria?

DR. MAKHENE: No. Actually, they were based on bacteriologic eradication.

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DR. RELLER: Throat culture, positive or negative.

DR. MAKHENE: Right.

DR. RELLER: Because I would like to ask Bill how much of that difference might be attributed to simply the reality of differences between penicillin and, especially, for example, third-generation cephalosporin. When one thinks about, for example, meningococcal eradication of carriage between penicillin and ceftriaxone, owing to whether the drug is in the superficial secretions, you might say.

DR. CRAIG: I would say that that probably could be an explanation. Clearly, I think, if you look at some membrane studies and look at penetration across membranes that don't have pores in them is that some of the cephalosporins will penetrate better than what one would see with penicillin.

Clearly, some of the third-generations have been able to eliminate meningococcal carrier state while penicillins have not. So I think some of that can clearly reflect penetration into secretions.

DR. RELLER: Given that, it raises the question of why do we treat group A strep pharyngitis. If it is early on, to shorten the clinical course in a small proportion of

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patients but, primarily, to prevent sequelae, what I would really want to know is do these categories of agents make a difference in either of those two, and I am not so concerned that there might be a difference in whether or not you could isolate the group A streptococcus after treatment.

We will come back to that having to do with the comparative agents because I wonder if the microbiology results are really giving us the right answer for what we really want to know.

DR. HENRY: Just one last clarification. On your post-therapy test-of-cure visit, the fourteen-to-eight-day time frame, where did that--why fourteen-to-eighteen days?

DR. MAKHENE: That is actually historically based on the fact that penicillin, before newer therapies and some of the shorter-course therapies, patients, for the most part, have been treated for ten days with the antibiotic of choice. So, to give time, again--there was a question earlier this morning regarding the time period to wait after treatment, to essentially just wait after completion of therapy and allow there to be no drug on board, and then do your culture at that point.

DR. CHESNEY: I am not sure if this is clarification or if we should bring it up later, but the

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issue is also with the test-of-cure visit. I assume that it is just growing the organism, not doing further subtyping, the same issue that came up with the repeated urinary-tract infection, because, remember, these patients get a new streptococcal infection.

DR. MAKHENE: Right.

DR. CHESNEY: So I don't know if we discuss that later. I just wanted to clarify.

DR. MAKHENE: At this point, yes; it is. We had some discussions internally in terms of what different reviewers have been doing in making that assessment, and, essentially, there is no serotyping that we are asking for. It is based just on isolation of the organism or evidence of eradication of the organism at the test-of-cure visit.

DR. CRAIG: Okay.

Dr. Christie?

Committee Presentation

DR. CHRISTIE: Thank you, Dr. Makhene for your comprehensive overview.

I have just two comments. The first one had to do with serotyping or PFG typing of the strains because, again, you wanted to find out if the pre-treatment strains and the post-treatment strains are homologous. Again, that question

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comes up but it was just answered.

The second one is the major question being posed to the committee regarding whether or not penicillin should still be considered as a first-line comparator agent bearing in mind, as we noted, from the studies you presented, that there are no higher rates of failures with patients treated with penicillin in recent years.

I just have a few comments with regard to that. The first thing is that, as we look at the literature, as far as I know, there have been no penicillin-resistant isolates of group A strep reported anywhere in the world. That, I think, is very important.

The second point, looking at the 50 studies, 50-plus studies, that evaluated streptococcal bacteriologic treatment, failures in oral penicillin over a four-decade period, two-thirds of these studies, serotyping of the group A strep isolates was actually performed to determine the similarity of post-treatment isolates with the pre-treatment ones.

Careful analysis of this subset of patients actually showed that the penicillin is just as effective in the beginning as it is today in treating group A strep pharyngitis.

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In the metaanalysis of the nineteen comparator studies with Dr. Pichichero, although he recommended that cephalosporins should be used primarily over penicillin, and should probably replace penicillin for group A strep pharyngitis, we notice that there are other people who recommend just the opposite, like Mike Gerber and colleagues like Stan Schulman.

Essentially, what they did is that they looked at the metaanalysis that was performed and found that it was seriously flawed. These gentlemen actually pulled out just three of the major studies among the nineteen which were properly done.

They were randomized, controlled trials which assessed patient compliance. They included consistent definitions for failure versus success. They included serotyping of the isolates to establish homogeneity. They also looked at all the patients who were enrolled, accounting for all the subjects, and they also looked at bacteriological cure rates as opposed to clinical cure rates.

Essentially, when they corrected for all of those factors, they found that the cure rates of first-generation cephalosporins exceeded penicillin by only 4 to 6 percent.

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So, based on that, it is still recommended that penicillin is the first-line therapy, or penicillin VK is still the first-line drug for group A strep.

Another concern they found with these trials is that quite a few chronic carriers with group A strep were apparently enrolled in these studies. And these persons were found to have possibly recurrent viral illnesses with colonization of the pharynx with group A strep. Because of this, this tended to overinflate significantly the apparent failure rate in the penicillin-treated groups.

For example, in one particular study, it was 19Êpercent for pen VK versus 10 percent for cefalexin. So, looking at the studies where the carriers were excluded, the bacteriological failure rates were then noted to be quite low and, therefore, I agree that carrier enrollment should be minimized, possibly to make sure we exclude those who have viral symptoms and especially those who have recurrent group A strep isolates from the back of the throat.

Other reasons for penicillin-treatment failures that have been suggested and studied include the fact that you may have poor patient compliance with penicillin which increases the risk for reinfection. And then there is the role of beta-lactamase-producing organisms in the pharynx

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like your Staph aureus, your H. flu, your Morexella.

Essentially, because penicillin does not eradicate these organisms from the pharynx, penicillin may well be inactivated by the beta lactams in these organisms.

Some have also suggested and some have proven, although this is still controversial, that if you treat the patient immediately once the patient is diagnosed with groupÊA pharyngitis, that could somehow ameliorate the immune response and, therefore, these patients are sort of set up for reinfection and relapse as compared to patients who you wait a little bit longer, say, two to three days before you start penicillin therapy.

Others feel that cephalosporins appear to be a little bit better at eradicating the group A strep carrier state if you compare these patients to those who just got penicillin alone. Others have suggested that some of the penicillin strains actually develop tolerance and that might be one reason for repeated infections.

Then, again, there are cryptogenic infections in the tonsillar crypts possibly making the drug not as available to those hidden organism as it would be for organisms that are elsewhere.

Then a patient could reacquire group A strep in

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the family environment or in a close environment and get reinfected that way as well. Others have also suggested that penicillins may even eradicate colonizers like alphahemolytic streptococci from the pharynx more readily and cephalosporins. Therefore, these patients may, then, become more susceptible to group A strep reinfection.

And so, with these reports of high failure rates, the question to the committee is is penicillin still adequate as a comparator agent.

Just one more comment before I stop. I think in the earlier studies, to go back to Dr. Reller's question, the trials were done--the penicillin actually was found to reduce sequelae, the long-term sequelae. So it is not just bacteriological eradication but it reduced sequelae whereas, in recent years, with the newer antibiotic protocols, they have shown that it eradicates the organism from the back of the throat.

But I am not sure that studies have been done to show that it reduces acute post-strep glomerular nephritis and rheumatic fever. So penicillin has been tried and tested and proven but the other antibiotics have not been tried and tested and proven.

I think that is really what we are trying to get

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at, reduce acute post-strep glomerular nephritis and reduce acute rheumatic fever, especially in the era of this resurgence of group A strep infections with increased virulence, perhaps, and worse disease.

Committee Discussion

DR. MAKHENE: The only comment that I wanted to make specifically to that issue is in the review of the references in the literature, it seems as if the only drug that has been specifically tested regarding the prevention of sequelae is parenteral penicillin. Those studies were done originally in the '50's by Wannamaker and Denny in military bases.

Then subsequently, later on in the 50's, they did further studies where they compared oral penicillin to parenteral penicillin but only looking at eradication of group A strep in the oropharynx but not specifically at prevention of sequelae.

Subsequent to that, as far as I am aware, there have been no other studies that have specifically looked at the prevention of the sequelae. So my reading of the literature and my understanding is that the only agent which has specifically been looked at for the prevention of post-strep sequelae is parenteral penicillin and those were

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studies that were originally done in the '50's, as I said.

DR. NORDEN: You are correct, but I think there is one addition, perhaps, to that and that is that there have been studies of chronic suppressive or chronic prophylactic therapy in people who have had streptococcal infection and rheumatic heart disease. Again, bicillin is the most effective probably because of compliance, but there is data with oral penicillin and also with procaine penicillin showing efficacy in terms of preventing further attacks of rheumatic fever.

You are right, though. I don't think there is any other primary data with original episodes of streptococcal pharyngitis. But I think you could extrapolate to some degree and say that it would seem logical that oral penicillin should be effective in preventing rheumatic fever.

DR. RELLER: Dr. Norden, are you comfortable for extrapolation to other compounds that have been shown to eradicate the organism but are not penicillins?

DR. NORDEN: Logically, I ought to be consistent. But I am not. But I have no basis for my discomfort and just feel that penicillin has been here for a long time. There is a lot of good data, I think, with rheumatic fever

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in prevention, prevention of further sequelae in people who have rheumatic heart disease which doesn't exist with the other agents.

Yes, they probably should work. There is some data with sulfonamides, also, which suggest that they worked for a period of time back in the early '50's, but there is no data for cephalosporins or macrolides that have looked at this. Part of that, of course, is the trend towards disappearance of rheumatic fever in the United States over a period of time which could recrudesce, as we know, at any time.

So, no, I am not as comfortable but I have no sound basis for my discomfort.

DR. CRAIG: I think my way of looking at it is that I guess I prefer being relatively narrow-spectrum. I think this gives the chance of using a drug which is directed primarily against the organism and then allows you, for other comparative agents, or new agents, which may have a wider spectrum, to see what other effects those drugs have in terms of toxicity, things like that, besides covering this organism, to look at others.

I think if you look at the Red Book, the pediatricians clearly recommend penicillin, erythromycin in

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the susceptible. However, I think if you look out at what is being used in the real world and go to the family practitioners, there is where you find a lot of the heavy cephalosporin use.

I know the CDC is on a big campaign to try and change some of that cephalosporin use back to penicillin. So I think it is still the drug of choice. The only thing that I would do differently than what you do is I would allow companies to do BID dosing instead of TID dosing.

BID dosing is what is actually recommended in the Red Book by the pediatricians. I think there are studies out there and I know that has been a frustration to some of the pharmaceutical companies where they have wanted to do a BID/BID and then they have to do a TID, and that really starts making it difficult trying to do a double blind.

So I would keep the drug the same but I would allow them to do a BID dosing.

DR. HENRY: On the surface, this looks like it should be a very easy study to do because you have got one site that you are culturing. You have got one organism you are looking for. And you have got a great comparator drug. But beneath that veneer is a really complex problem because it is going to be hard to sort out and disallow or exclude

the carriers because you may be relying on a parent to say, "Well, I don't know. My kid, when they have strep, get treated so I assume it is real."

So you are not certain, sometimes, who the carriers are. That really kind of falls over, then, into looking at your microbiologic outcomes because you may have someone who does truly recur with a different serotype. Is that a carrier? Is that a recurrence? Is it a recurrence with the same strain which would be relapse because you haven't eradicated it from the tonsillar crypts.

Some kids' tonsils look horrible and you know that the organism is probably still in there somewhere. But I think you have got this whole concept of who is the carrier, who has simply got recurrent disease from a new isolate.

So it really blurs and it is going to be really hard to sort out the data if you are not certain that you have excluded the carriers up front, and then you have got these people who persist with what, the same serotype, different serotype, recur? I don't know that you can really come to good conclusions without looking at some serotyping evidence which complicates what, on the surface, should be a very simply study.

DR. CRAIG: Although getting serotyping in the

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United States is very difficult. I only know of one laboratory in the United States that does that. And the charges are fairly hefty.

DR. HENRY: So a private lab could make a lot of money.

DR. CRAIG: Yes. If there was some competition out there.

DR. RELLER: Fortunately, despite all those difficulties, 85 to 90 percent of people, after getting an appropriate course, may include BID of penicillin, the organism is not there. So the questions I asked earlier would like to emphasize what I think is probably a strong consensus around the table of pushing in every way possible to have new agents compared against penicillin.

All of those metaanalyses, to me, do not provide data that would suggest that there is any reason not to use penicillin as the primary and most important comparator for all of the benefits that have been expressed around the table.

There should be incentives. If you believe the metaanalyses, it would make it easier--

DR. CRAIG: My advice to the pharmaceutical companies would be to keep their strains. Then, if it looks

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like their drug is doing worse than the penicillin, that is time, then, to do the serotyping and things like that. But I am not sure that the cost of doing it would justify doing it routinely.

Obviously, it is always nicer data when you have all of that information, but it could increase quite a bit the cost for a therapy where, really, many of us and the CDC, pediatricians and everything are pushing for more penicillin use, not more of the new drugs.

DR. CHESNEY: Just a question about the streptococcal fever under the inclusion criteria. My understanding in the few children I have seen with this, the organism actually grew from the anterior nares and not always from the pharynx. Would that area be cultured? Also my assumption is if they didn't grow strep, they would be excluded from the study.

DR. MAKHENE: That they would be excluded from the study? You are saying because they didn't grow from the oropharynx?

DR. CHESNEY: Yes. These children are hard--this description is that of any viral syndrome in a child.

DR. MAKHENE: Right.

DR. CHESNEY: So, presumably, when the culture was

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negative, they would be removed from the study.

DR. MAKHENE: Correct. Yes; they would.

DR. CHESNEY: And the cultures would be from the nose and from the pharynx?

DR. MAKHENE: We would expect that they would have a positive culture from the throat in order to be eligible for enrollment in the clinical trial.

DR. CRAIG: Any further comments, questions? Someone from the audience?

DR. LEROY: Bruno Leroy, HMR. Regarding the dosage and dosing of penicillin, could you clarify a bit more what you could recommend as a dosage and dosing? The recommendation of the American Heart Association, I think it is 500 milligrams TID, three times daily.

Would it be the gold standard for you for a comparative agent because it is not approved, per side effects, in the U.S. The dosage approved is 250, three to four time daily which could be considered as insufficient to prevent rheumatic fever for the American Heart Association.

500 milligrams three times daily is accepted for other indications for penicillin. So what would you recommend to clarify--

DR. CRAIG: I think if you look at the Red Book,

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and I would have to get it out, but I am pretty sure that BID is actually the recommended dose and they acknowledge that it is different than the American Heart.

But I would have to look at that. I don't have my copy of the Red Book, but I am pretty sure that they allow, I think it is probably 500, 250 to 500, depending on how small the kid is, BID.

DR. MAKHENE: Are you asking specifically for acute strep pharyngitis, or when you are saying American Heart, are you referring for acute pharyngitis?

DR. LEROY: Acute pharyngitis in adults.

DR. MAKHENE: In adults, it is 500 BID, as Dr. Craig just said. Pediatric patients, 50 mg/kg/day, also BID.

DR. LEROY: So you confirm that only one study is necessary, not two.

DR. CRAIG: What did you say?

DR. LEROY: Only one study would be necessary. You confirmed that only one study versus penicillin would be necessary.

DR. MAKHENE: Yes.

DR. LEROY: Thank you.

DR. CHIKAMI: Let me clarify that. The intent of

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what was described in the points to consider document was that one adequate and well-controlled trial be done with some sort of--with corroborative data. In the points to consider document originally, there was the proposal that additional information such as pharmacokinetic data be provided to provide supportive data.

If that were not available or not provided or if a second adequate and well-controlled randomized trial was done, then that subsequent data, or that other corroborative data, would not need to be submitted.

So I think that the intent is corroborative data for the one adequate and well-controlled study be provided. If the committee feels in the comments that Dr. Norden spoke to and Dr. Rodvold that, in fact, such data that pharmacokinetic data, or however it is stated in the document, in fact, doesn't provide really corroborative data to make the determination of safety and effectiveness, then we will have to rethink that recommendation.

Often what we see in the course of clinical development is that two trials are done. For example, a trial in pediatrics and a trial in adults. But, again, the general intent is that data from one trial be corroborated with some other information.

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DR. NORDEN: Thank you, Gary. I think the pharmacokinetic data will provide you no corroborative information that I would find helpful. I think the real answer has to come from the clinical trials and you have to rethink whether you really need--I don't think you really need two trials in this indication, personally.

But I often didn't think we needed two trials.

DR. CRAIG: If you look at, for example, penicillin pharmacokinetics, what used to be done is people would stop after three or four hours and that is all they would get. If you look at that, all you pick up is the very rapid half life of penicillin. But there is a later, slower elimination phase with a half life of about two hours so that if you are looking at a very susceptible organism like group A betahemolytic strep, you are above the MIC 100Êpercent of time, even given the drug Q 12 hours.

So you always have the problem, sometimes, the pharmacokinetics of not looking at the full picture. That was, really, one of my favorite publications where, in 1988, I think, we published an article on the pharmacokinetics of penicillin in normal volunteers.

You would think, by that time, everything should be known 40 years later about how the drug behaves in normal

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volunteers. But everybody stopped relatively soon as far as doing the kinetics and never followed the drug out for a longer period of time.

So there are things that I think pharmacokinetics can be helpful for in trying to insure that the drug stays around long enough in serum which would, then, reflect it staying long enough, probably at the site of infection.

But, looking at the tissue and grinding up the tissue where you are mixing intracellular and extracellular fluids is what I have more of a problem with, and using that as a definite indicator.

DR. CHIKAMI: We will clearly have to rethink that issue as stated in the document and have some further internal discussion about that issue.

DR. MURPHY: There is some guidance also out on when one study might be useful. In other words, there are parameters one would want to meet such as very clearly demonstrating efficacy, a multicenter study.

If you come in with one study that is not very clear in its difference, you have some problems with the study, you basically are taking a risk. It is not that we wouldn't consider it. I would refer you to the guidances describing when one study might be applicable.

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DR. HENRY: I guess I have two questions or comments. The first thing, when you refer back to your paper in 1988 with penicillin pharmacokinetics, were there kids included in that, because I think the metabolism of drugs is clearly different.

DR. CRAIG: No.

DR. HENRY: So that was based solely on adults.

DR. CRAIG: Right.

DR. HENRY: Which leads into the next comment and that is I think that there have to be separate studies for adults and kids. I think some of the entry criteria are going to be different. I don't think you see the incidence of carriage of group A strep in adults that you see in kids.

I think it is going to be a lot more difficult to sort that out. Clearly, if you had one large study that had all age groups included, you would have to break out the data and stratify it for analysis.

So why not have two good studies but one done in a pediatric population and one in an adult because, to some extent, it really is a little bit different. Certainly, the pharmacokinetics of penicillin might be different.

I still use penicillin for group A strep, at least the first go around, and I do dose it three times a day,

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even though it is very difficult, sometimes, for parents to comply. So I would be a little uncomfortable with one large study and decisions made based on that composite population.

DR. CRAIG: I would not have as much concern. I, also, look at it, since we are trying to say penicillin is really the drug that should be used, at least that is what many of the organizations are saying, to force a lot of study for something that you hope is not going to be used except occasionally for the penicillin-allergic individual, I have a little bit of concern with.

I think a very good single, large, multicenter randomized trial would answer the question for me.

DR. RELLER: This is such an important pediatric disease. Why not say that if you want your drug approved for adults and children, you need two studies. If you have one big multicenter one in children or one big multicenter one in adults, you could get half of the pie. But you need two studies properly done to get the indications for adults and children. It is a possibility.

DR. HENRY: Oftentimes, studies that are done in adults, people say, "Well, if it works in adults, it should work in kids. Why not do it the other way around? The pediatric situation is far more complex. If it works in

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them, by reference, it should work in adults. So I think you have to really weigh the study if you are going to do one on the side of the pediatric, or just do a very good, large pediatric study.

DR. CHESNEY: Rather than two separate studies, let me ask, do you have any requirements for numbers of children and numbers of adults that are included? In other words, could you end up with a study where you had five children and 500 adults?

DR. CHIKAMI: My experience has been that, in this disease, adults and pediatric patients are studied separately and that, in fact, in the course of the development of products for this indication that there are usually two large studies done, one in the pediatric age group and one in the adult age group.

So, in fact, many of these issues that are being discussed are usually covered in the development of most products for these indications.

DR. CRAIG: Usually, they are going to do the adults first and pediatrics sometimes follows behind.

DR. ALBRECHT: But I think with antimicrobials, we have long recognized the need to do studies in children. Certainly, when an infection is one that is common in

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children, like otitis or pharyngitis, we have encouraged, and actually companies have conducted studies in children in those specific indications.

I think we have a problem in other areas where disease is not as common in children and then, and I don't want to belabor it, we mention it in the general considerations document. There are now provisions. There was a regulation in 1994 which allows for information from adults to be extended to children if that is appropriate.

So, in those scenarios, we may be approving use for children on smaller numbers, but we would not do it in cases where it is not just reasonable but even responsible to study a drug's effect in children.

DR. CRAIG: Anything else? If not, we are done with the morning session. We actually will meet back here at 1:30.

[Whereupon, at 12:30 p.m., the proceedings were recessed, to be resumed at 1:30 p.m.]

A F T E R N O O N S E S S I O N

[1:40 p.m.]

DR. CRAIG: We are going to have a very busy afternoon. We are going to start off the afternoon talking on early Lyme disease. The FDA presentations will be given by two people, Janice Soreth and then Susan Altaie.

Early Lyme Disease

FDA Presentation

DR. SORETH: Good afternoon.

[Slide.]

DR. SORETH: I am Janice Soreth and I would like to start this afternoon's discussion on Lyme disease concentrating on aspects of clinical trial design. Sousan Altaie will continue with microbiologic considerations, and our invited consultant, Dr. Raymond Dattwyler, from Stonybrook, will serve as consultant with some particular and specific issues that we will ask him to comment on.

[Slide.]

As an indication, we have viewed Lyme disease as three bullet points, the first being early Lyme disease or erythema migrans, a localized infection; the second indication, early disseminated Lyme disease, which has as a subcategory meningitis, for if companies wanted an

indication for dissemination with meningitis, they would need to study meningitis, and thus the reason for that subcategory; last but certainly not least, late Lyme disease. We are not going to talk about that today. I am not sure I know what it is, and we are also not going to talk about early non-Lyme disease for which there is an epidemic in New Jersey right now. At least that is what Dr. Norden told me before lunch.

[Slide.]

Lyme disease begins as a local infection when an ixodid tick inoculates Borrelia into the skin of a subject. The early sign of the disease is that of a round, red lesion that is referred to as erythema chronicum migrans or simply erythema migrans.

EM begins as a red papule or macule and expands over a period of days or even weeks to form a large, round lesion. We tend not to see this happening anymore because people, particular in endemic areas, are so attuned to the disease, they don't want for it to get big and red and round and expand, but we know by natural history that is what happens.

Lastly, EM is often accompanied by a flu-like illness with nonspecific symptoms of myalgias or

arthralgias, fever, headache, stiff neck perhaps.

[Slide.]

To give you some appreciation of the size of the tick that we are talking about, we have the edge of a U.S. dime, and as you can see, the ixodes scapularis tick fits pretty much across the D and I and the M of a dime. It is small.

[Slide.]

Here we have a comparison of adult male and female ticks, and the nymph and larval forms, as well.

[Slide.]

So that you can appreciate where the deer tick or ixodes tick fits in relation to other ticks, on the left side of the slide you have the black-legged or deer tick, much smaller than the American dog tick with which you may be more familiar, and the Lone Star tick on the far right.

[Slide.]

Oh, I did load it at lunchtime, but I forgot to give it to you. This was a movie of a tick running across the screen, but the linking file is gone.

[Slide.]

Early Lyme disease. The diagnosis rests on clinical grounds. I can't emphasize this enough. Serology

can help, it can confirm, but it should never be the basis of determining that someone has early Lyme disease, whether it is a registration trial or whether someone is in your office presenting with something that might be early Lyme disease.

[Slide.]

Serology again is often negative early on in infection, and furthermore, patients treated for early Lyme disease can relapse and still be seronegative. This is work that has come out of Stonybrook and relatively recently published wherein, in a trial for early Lyme disease, patients who were seronegative despite some very convincing evidence of objective signs and symptoms for Lyme disease initially got better by treatment and then went on to relapse, and remained seronegative.

So again, in the setting of a registration trial, we would not view serology to rule in a patient at the beginning of the trial, and we would also not depend on serology and seroconversion later on in the trial to say aha, now, they are relapsing from Lyme disease. You don't have to have positive serology to have this disease.

[Slide.]

What happens in patients who are not treated? I

think there are three of them in Oklahoma now, but EM will fade, usually by four weeks, often sooner, and as the infection spreads, there can be secondary EM lesions, neurologic abnormalities, lymphocytic meningitis, carditis, and/or rarely acute arthritis.

Going on to late Lyme disease, what we have seen in patients is a chronic meningitis or perhaps more commonly meningoencephalitis, encephalopathy, peripheral neuropathy, migratory polyarthritis, and/or acrodermatitis, which I believe the acrodermatitis being more common in Europe than in the United States. Is that correct?

DR. DATTWYLER: Yes.

DR. SORETH: Next slide, please.

[Slide.]

Various staging systems have been proposed for Lyme disease. What I have put up here is a classification system that was initially proposed by Ava Asbrink from the Karolinska Institute, and it pretty much corresponds with how we have chosen to label the indications for the infection: Early infection/Stage 1: Localized EM; Early infection/Stage 2: Dissemination. She did not break out a separate category of meningitis, as we have. And lastly, Late Infection/Stage 3: Persistent infection.

[Slide.]

The study considerations for registration for drug for early Lyme disease or EM are as follows.

We recommend two trials, ideally double-blinded, randomized, multicentered, prospective study design. Placebo-controlled trials are not appropriate. The choice of the comparator, we would like if companies would discuss with us. When double-blind trials are impractical, then, we would ask for an investigator blind to trial, because some of the endpoints are subjective with this disease, so as much blinding as possible is really what we would like to see.

[Slide.]

The inclusion criteria are as follows. The erythema migrans should be physician documented and photographed preferably with a ruler in place, male and female patients of any age may enter.

In practical terms, children have not been studied systematically in early Lyme disease trials, but we have had in-house our data on adults. If a company were to have a trial enrolling patients of any age, we should just ask to look at the pediatric and adult populations separately.

Exposure to an endemic area is a must, and we have

strongly encouraged a 2-millimeter punch biopsy of the EM lesion. We have encouraged it, we usually haven't gotten it, but I think that techniques of punch biopsy, as well as culturing techniques, have improved to the extent that it is now reasonable, not only to ask for this, but also to get it.

[Slide.]

Exclusion criteria are as follows, and for the most part, these exclusion criteria are there because it becomes very difficult to tease out whether or not patients are having trouble with their Lyme disease or having trouble from antecedent arthritis as an example, so that is really the basis for many of these exclusions.

Active arthritis, signs and symptoms of CNS infection, meningitis, meningismus, or 7th nerve palsy, all of those would indicate that you are beyond the realm of early localized Lyme disease and you are into disseminated, and that is a different trial.

Heart block, history of any cardiac, rheumatic, nervous system, collagen vascular or immunodeficiency disease.

[Slide.]

Use of systemic antimicrobial active against B.

burgdorferi within the previous 10 days before enrollment. Why 10 days? It was a round number.

Concurrent systemic steroid therapy, antimicrobial treatment for Lyme disease during the previous 12 months, because again if symptoms crop up later on after treatment for this particular episode, you are not going to be sure whether you have relapse from an antecedent infection versus your current infection under study, so just better to exclude those patients up-front, and we have data now that help us to appreciate that very often there is coinfection with Babesia or Ehrlichia.

[Slide.]

Assessments are as follows: pre-therapy, on therapy, end of therapy, post-therapy. The on therapy, by and large, antimicrobials in early Lyme disease trials have been given for two to four weeks, so let's just say three weeks on average, and we would like to have the patient be seen about halfway through the drug course to make sure everything is going okay.

The end of therapy assessment is usually within a week or so after active drug therapy has ceased. The post-therapy assessments are meant to capture information shortly after the patient has completed their course of

antibiotics and then later on, because we know from the published literature and other clinical experience that patients can take a while to relapse.

[Slide.]

This slide should be titled "Per protocol." Short-term efficacy. In order to be evaluable for short-term efficacy, to be part of the per protocol analysis, one needs erythema migrans that was physician-diagnosed, 80 percent or more of the medication needs to have been completed, and some documentation of that either via a patient diary or urinary assay.

There should be a clinical evaluation during treatment. I think if that is skipped for some reason, I don't think that that would be any major problem, but the patient needs to be seen within about a week post-therapy and also a month post-therapy, and there should be no intervening courses of antimicrobials that would have activity against Borrelia.

[Slide.]

This should also say "Per Protocol." For long-term efficacy, well, you need to have it evaluable for short-term efficacy and have clinical assessments at some reasonable period of time between that first month off of

therapy and out to 12 months.

As an example of what that might look like, clinical assessments at 3 and 12 months after completion of therapy, with a telephone call at 6 and 9 months. Obviously, if during the telephone assessment there is reason to be concerned about the patient, then the patient would be brought back in for full physical exam and further intervention if needed. Of course, no intervening courses of antimicrobials that have activity against Borrelia.

[Slide.]

For the short-term efficacy evaluation, we basically categorize three outcome responses. The first is that of early response where there is resolution of EM and any objective signs, together with a greater than 75 percent reduction in symptoms by the one-week post-treatment visit, that is, by the end of therapy visit, maintained through that one-month post-treatment period.

Let me just make mention of something I meant to make a slide on. Part of the protocol I think should come with some assessment by the patient of their symptom score and severity.

What some investigators have used is a visual analog scale, so that the patient is determining at each

visit that the symptoms they initially presented with, which they characterized over here on the visual analog scale, are now moving back to here, and then one can quantify that visual analog scale to come up with this better than 75 percent reduction in symptoms.

I think that is important given the nonspecific nature of a lot of the symptoms, aches and pains and fatigue, and so forth, which any of us might have on any day, maybe like today, so I think it is important to build that in up-front in the protocol. When it hasn't been, we see people going back and trying to superimpose it retrospectively, and it is just a lot cleaner to do it up-front. So, early response as your first short-term assessment.

[Slide.]

Well, what about those people who they get better, but not as better as some of the other, because all early responders are not equal. So, we came up with early partial response akin to improvement, resolution of the EM, but there is incomplete resolution of the signs or symptoms, so you have a visual analog scale where you are between 50 and 75 percent essentially at the one-month post-treatment visit, and lastly, for that short-term evaluation, failure.

[Slide.]

I wrote here "persistent EM," but as Ray and I were chatting, you really don't have persistent EM. If you do nothing, EM fades by four weeks or sooner, so what you are really looking for is persistence of objective signs, other objective signs, or symptom reduction that is less than 50 percent on that visual analog scale.

Why not just call it "cure improvement and failure"? Because this isn't really the test-of-cure, if you want to use those terms. This is a look early on with patients, and we want to see what happens through the 12-month assessment post-therapy to really say this patient is better, this patient is not better.

[Slide.]

So, in the long-term evaluation, then, it boils down to two responses, cure and failure. Cure would be those early responders, either partial or complete, who maintain their reduction in symptoms through that 12-month post-therapy visit and have no development of any objective signs like a hot, swollen knee, for example, and failure, then, the early failures from the short-term evaluation carried forward, together with any patients who look like early responders, partial or complete, but who go on

subsequently to develop objective signs or a constellation of symptoms that require retreatment.

I would like to welcome Dr. Sousan Altaie to the microphone now, and she will continue with microbiologic considerations, and then we will wrap up with some questions and comments from Dr. Dattwyler.

[Slide.]

DR. ALTAIE: I would like to this afternoon address some of the issues that are microbiologically relevant. Since this is not a usual bacteriological process, I would like to touch on laboratory qualifications, how to obtain the punch biopsy, and following that, by isolation of Borrelia burgdorferi and what is required to culture that, then, in-vitro antimicrobial susceptibility testing, how that should be done, and the serologies, addressing serologies in Lyme disease.

[Slide.]

The laboratory should be operating under rigorous quality assurance programs, and they should be participating in recognized inspection and proficiency programs.

[Slide.]

The microbiologists themselves should be experienced in isolating Borrelia burgdorferi and being able

to store and retrieve it, and do susceptibility testing on it. We like to see, however, since these are not very standard procedures, we like to see all the operating procedures and protocols to be submitted to us in as much detail as possible.

[Slide.]

To address the punch biopsy and how to collect and transport the samples, I would like to say that the border of the EM, the leading border of the EM lesion should be identified, and then moved in 4-mm interior to the border, and do the punch biopsy there. That should be a 4-mm punch biopsy.

[Slide.]

This punch biopsy can then be placed into a Stoenner-Barbour-Kelly modified medium, referred to as BSK-II medium, which contains antibiotics, and these antibiotics are there to prevent contamination overgrowth from the specimen that is naturally skin.

So, the antibiotic-containing media is crucial to being able to isolate these organisms. Then, you take the specimen and place it in that media, and it can stay at room temperature for up to one week, so otherwise facilitating the possibility of batching this for shipment and processing

in the central laboratory.

[Slide.]

I need to say a few words about the media itself and how important it is to have this media to have a productive culture. The media contains bovine serum albumin fraction V, and all the spirochetologists know that BSA contains some unknown inhibitory material that is present in some lots and absent of the other lots.

So, most spirochetologists that want to grow Borrelia, they screen lots of batches of BSA and then pick the batch that gives them the best result in culturing, and utilize that to make their media.

A media that is prepared with an appropriate BSA should be able to grow 10 organisms within two to three weeks, to a degree that is easily visualized in dark field microscopy.

[Slide.]

The other issue in preparing the media is the high quality of the distilled water that should be used in that media, and that the media should be fresh, and that means less than two months old.

The incubation temperature should be at 30 degrees for 12 weeks, and reading the cultures at no earlier than

three weeks, repeating reading until 12 weeks.

I suggest that cultures before being dismissed as negative to be taken into a PCR assay performed on the culture media and the culture tissue, and then discard them as negatives, because the experience is that if you do a PCR, if there was a bug that was being inhibited or overgrown, or whatever, you tend to pick it up in a PCR assay if you don't pick it up with the dark field microscopy, so I suggest that would be something to do before discarding cultures as negatives.

[Slide.]

Susceptibility testing should be performed on any isolate that is obtained from the EM lesion before treatment, and that susceptibility should be repeated for a patient who failed treatment and come back with an EM lesion that is visible and culturable.

[Slide.]

This MIC, we need a 90 to address that issue of how to use this MIC data. This MIC data should be analyzed to compare the MICs pre- and post-treatment, and this will allow us to detect any resistance if it is to be present.

[Slide.]

Bacteriologic efficacy should be determined at

each MIC to allow the determination of a breakpoint above which treatment failures are expected.

[Slide.]

To address the serology in Lyme disease, I like to state that serology should be used to confirm, not to make, the diagnosis of Lyme disease, as Dr. Soreth mentioned. IgM, there is quite a bit of reasons for that, because IgM does not go up until more than four weeks post-infection, and the IgG level may not be elevated until 6 to 8 weeks post-infection.

[Slide.]

Also, antibody results may be falsely negative in early Lyme disease for that reason, and the antibody results may be falsely positive because of the cross-reactive antibodies from Epstein-Barr virus infections, from rheumatoid arthritis, or from other spirochetal diseases, and so the false positivity rate is pretty much great.

On top of that, to complicate issues, all the ELISAs have inter- and intra-laboratory variations, and it makes it difficult to interpret the ELISA results.

[Slide.]

Because of this, every effort should be made to test all the serum specimens from an individual patient on

the same day, within the same run, in the same laboratory, to alleviate some of these discrepancies or intra- and inter-laboratory testing result variations.

All the positive ELISA or IFAs, the serology should be confirmed by performing a Western blot assay. This is actually a two-tiered criteria that was advocated by Dearborn conference and CDC supports that.

[Slide.]

So, what is a positive Western blot? A positive Western blot is if it's an IgM Western blot, it should have two of the following bands on the blot, and they are listed up there, OspC and BmpA and flagellar genes.

Then, IgG has 10 bands, and 5 of those bands should be present before an IgG Western blot is called positive. I would like to add that these bands and their presence and absence is quite controversial at this time. There are other bands that are recommended. There are some bands that are suggested to be omitted, but currently this is the standing standard until the next standard comes about with more experience.

[Slide.]

This is for our consultant. We would like to ask Dr. Dattwyler to address the comparator chance for us, what

would be an appropriate comparator for doing the early Lyme disease studies.

The other point that we would like for him to address is how vaccinated. We know that there is the vaccine, OspA vaccine being processed in the process of approval, and how would that vaccinated patient be diagnosed as far as serology is concerned, and how this vaccine would influence the serology test at that time.

[Slide.]

I would like finally to thank my colleagues in the Microbiology Group in the Division of Anti-Infectives. Dr. Sheldon, who is our team leader, and he never stops supporting us. Fred Marsik, Harold Silver, Peter Dionne, and Dr. King are to be appreciated for their input.

Thank you.

DR. CRAIG: Questions, clarifications? I guess one question I would have, what is the frequency of resistance among various drugs or is there any resistance documented?

DR. ALTAIE: At this point, there is no resistance documented.

DR. CRAIG: So, this is essentially a fishing expedition in terms of making this a requirement to try and

see if you can find some resistant organisms, is that it?

DR. ALTAIE: This is actually being proactive, I think.

DR. CRAIG: I mean do we have reasons to suspect that resistance develops in spirochetes very frequently?

DR. SORETH: No, and it is not a requirement that a patient have a biopsy in the first place. We are trying to encourage sponsors to take a biopsy of an EM lesion just to collect more information.

One of the biggest experiences we have now on microbiologic documentation of early Lyme disease is in vaccinated patients. Actually, the public presentation of the SmithKline vaccine recently by our Center for Biologics gave Alan Steer the opportunity to comment on the number of patients that were biopsied post-vaccination who developed erythema migrans, and I think the rate of culture positivity was on the order of 85 percent for recovery of Borrelia, so we finally have, I think, good punch biopsy techniques, good media to grow the spirochete in, and willing investigators and patients in order to look at the microbiologic aspects of this disease, which in earlier trials were lacking because no one was biopsied.

DR. CRAIG: But no standardized susceptibility

tests?

DR. ALTAIE: There is no standardized susceptibility test, but there is actually a standard susceptibility test. It is not a consensus, it's a well-controlled microtiter or macrodilution method, and it is acceptable currently. People do use it even though it is not a standard that NCCLS puts on the table, but it is a well-standardized method that people do use.

DR. DATTWYLER: There is a problem with susceptibility testing, though. The time killing curves in spirochetes are very critical.

DR. ALTAIE: That's right.

DR. DATTWYLER: When one looks at the effect of antimicrobials, especially beta lactams, if you wash away the beta lactams, say, after 24 hours, you can easily regrow a spirochete whether it is T. pallidum or Borrelia burgdorferi, so time killing is critical in the analysis of this, and that has not been standardized.

To answer your question, there is no known resistance that has developed in this organism. The organism is not under pressure because it is a zoonosis, so there is no human pressure out there. The host populations are not being subjected to antimicrobials, although there

are whole classes of antimicrobials that this organism is not sensitive to.

DR. CRAIG: Any other clarifications? Yes, Dr. Henry.

DR. HENRY: When you talked about doing PCR out 12 weeks on negative cultures, do you need to wait that long to do it? I mean the 12-week time I assume is based upon punch biopsies of EM lesions, and it has really taken 12 weeks. I mean is there some reason not to do it sooner?

DR. ALTAIE: No, you can do it sooner, but if you are not looking for a complicated procedure or an extra step, you can actually just go up to 12 weeks and still be able to detect positives if they were negative at 6 weeks, and even at 9 weeks, if you read them at 9 weeks, and they are negative, sometimes they are turn positive at 12 weeks, so it is the issue of what was the load of spirochete when you put it in, how favorable an environment was for it to grow, and so I hate to throw out a culture if I am not doing PCR before 12 weeks.

DR. CHESNEY: It seems like this is the ultimate clinical diagnosis because people are picking them up before they have even started to expand, and I even used to be challenged when they were just beginning to expand, and

without any microbiologic requirement and with no serologic confirmation, I would be interested to hear how you can be sure of the diagnosis.

I realize you have a picture, but even then if it is a very early lesion, and I know physicians in endemic areas are very skilled at making this diagnosis, but it is just a little unnerving that we are dependent on one little, red lesion.

DR. ALTAIE: That is true.

DR. DATTWYLER: I wouldn't be so sure that they are so skilled. Lyme disease is overdiagnosed and underdiagnosed. It is really quite poor. I can tell you that there are people on Long Island, which is heavily endemic, who declare themselves, including pediatric infectious disease specialists, who miss erythema migrans.

One guy at our hospital was teaching the house staff that erythema migrans was always a flat lesion, that if there was any edema in the lesion that it couldn't be erythema migrans, so we have some culture-positive lesions to show him that that is not true.

Committee Presentation

DR. DATTWYLER: I could make some comments on PCR. One should probably suggest more than one probe, both the

genomic and plasmid probe, and that is probably important because if you just do one probe, you might miss it.

If I could address some other issues, too. The issue of the punch biopsy, a 4-mm punch biopsy requires a suture. The standard has now dropped down to 2-mm punch biopsies, and the culture yields on those in good hands are 85 to 90 percent.

The alternative to that is an aspiration technique that was published by Gary Wormser, and that is injecting saline and then sucking back on it, and the yields on that are 40 to 50 percent, and not as good as punch biopsies, but certainly, as an alternative to a punch biopsy, might be something that would be suggested.

The laboratory qualifications I am afraid would exclude both Dr. Alan Steer's lab and my lab because neither one of us participate in rigorous quality assurance programs that I am aware of. That is more for commercial labs. We both can be vouched for by CDC, since they use us as standardized labs, so I think it would be okay.

The other thing about BSK media, Sigma now makes it and does quite a good job, and frankly, we get better culture yields using Sigma's media than making our own. I hate to admit that, but my technicians are not as good as

Sigma's quality control, so that might be a thing that a good commercial source of BSK media I think could be acceptable in that.

The thing about serologies, I think that the old data on serologies is that it took a long time to seroconvert, and I think that represented the poor quality of the serologies.

Using more modern techniques at presentation, about 30 to 40 percent of culture-positive erythema migrans lesions are IgM positive by CDC criteria, and CDC criteria is an adaptation of the criteria by Dressler, et al., and I am on that committee. It was only meant to be an interim recommendation until something better came along.

People are working on recombinant-based assays now. One of the great difficulties--and we read a lot of Western blots--is that there is a lot of extraneous bands on Western blots, and we have no idea what they are, and even the bands that are in the CDC criteria, some of those are not well characterized at this particular point in time, so I think that with the advent of new recombinant-based assays, I think we should also leave room for that in any criteria out there.

As far as the specific questions that were

addressed--I don't know if you want to put the consultant's questions up there--what comparators to use.

The two best study drugs for early Lyme disease are amoxicillin and doxycycline. They have been used, by and large, in most studies as comparators. The earliest study was published by Alan Steer and his colleagues when he was still at Yale, compared penicillin, tetracycline, and erythromycin, and those are no longer acceptable.

I think that all of the more recent studies have either used amoxicillin or doxycycline as the comparator agents, and they have a very strong track record of efficacy that is demonstrated in multiple papers.

The only approved drug for Lyme disease from FDA approval is cefuroxyacetyl, but if one looks at those studies that they were compared against, doxycycline or amoxicillin, so I think that that still should be the major comparator.

As far as duration of therapy, as Janet said, two to four weeks has been the standard, so usually three weeks seems to have been adopted, although I think that is somewhat arbitrary.

The question of serologic testing in vaccinated individuals, the SmithKline Beecham vaccine that has just

recently been discussed by FDA is a recombinant, protein A vaccine from Borrelia burgdorferi [sensostricto] strain. It will cause all people to be positive in IFAs and whole cell ELISAs, thus eliminating them from consideration as a screening assay or an assay to follow.

We, in my laboratory, our group at Stonybrook has been working on recombinant-based assays, and we have assays that lack OspA epitopes, so that they are efficacious in vaccine and vaccinated individuals.

The alternative to that is Western blot analysis. Unfortunately, individuals that have been vaccinated, you would expect perhaps they would only have an OspA band on Western blot. It is not always the case.

Borrelia expresses a number of highly cross-reactive proteins including the flagellin and some common bacterial antigens, so that the norm in many individuals is to have multiple bands on a Western blot, and may be difficult to interpret in some hands.

So, I think that as things improve, we should leave room for these recombinant-based assays, whether they are ELISA or some sort of an immunostripe assay, and that might be quite helpful.

Serologies, as I said, are getting better although

there is no direct correlation between clinical outcomes and serologies.

I think that is the major points that can be made.

Committee Discussion

DR. CRAIG: So, overall, trying to get microbiologic diagnosis sounds like it would be very good.

DR. DATTWYLER: Yes. I think that would be very good, and I think with modern techniques, that it can be done. The other thing that one might consider is direct PCR of the biopsy specimen. We routinely PCR from skin biopsy and have good success.

The other thing that I think that is critical, that Janet brought out, was that I think people focus on Lyme disease and forget that there are other tick-borne infectious diseases that are in these endemic areas. Certainly, Babesia and Ehrlichia are becoming more common, and I think requirements for those should be made.

Borrelia and these other organisms are carried by the same tick. HGE and Babesia carriage rates in our ticks are quite high in the Northeast, so that it is not uncommon that 20 to 30 percent of the ticks that are infected with Borrelia have another pathogen, as well. I think that is something to be considered.

DR. CRAIG: Dr. Norden.

DR. NORDEN: Ray, in the patients in the vaccine trials, those individuals who were vaccinated and got disease, was there anything different about their disease clinically, did they get anything atypical or does it look just like--

DR. DATTWYLER: It looked like typical disease. I didn't participate in it, but I am on the vaccine that FDA handled, evaluated that vaccine, and there was no clinical difference.

DR. NORDEN: So, that wouldn't be a problem then.

DR. DATTWYLER: That does not appear to be a problem.

DR. CRAIG: Dr. Henry.

DR. HENRY: Because of the possibility that patients could also have Ehrlichia infection or Babesia infection, does that mean that everybody who enters into the study has to have serologic testing for both of those organisms, as well?

DR. DATTWYLER: It depends upon how sophisticated the individual making the diagnosis was. Certainly, the patients with these other diseases tend to be sicker than patients with local erythema migrans and local Borrelia

infection, but it might be something that one would desire.

Serologic assays for both of those are not well worked out. We routinely do when we make the diagnosis of Babesia, it is on smear, and then we have PCR set up in my laboratory to evaluate people for Babesia infection.

I know also that David Persing of the Mayo Clinic has that capability, as well. I think that at this point in time, there is limited laboratory capabilities for some of these other organisms. I don't know that the current commercial assays are adequate. I think they are still a little primitive. So, it depends on where you do it.

DR. HENRY: And that is the problem because I think maybe in the beginning, you could feel comfortable saying that this is Lyme based on the skin manifestations, but if somebody comes back in follow-up and has symptoms that have persisted or symptoms that have gotten worse, it may be because they are coinfected and you have treated Borrelia, but you haven't treated Babesia or Ehrlichia, so I think if you are going to collect the data, you almost have to collect it at entry, so you know how to interpret recrudescence of symptoms at one of the test-of-cure visits or later.

DR. DATTWYLER: I quite agree. I think that is a

very important point, and certainly, Ehrlichia is not susceptible to beta lactams, and it would be susceptible to tetracyclines, and Babesia, I don't think we know how to treat at this particular point in time. Clindamycin and quinine doesn't work very well.

DR. CRAIG: Other comments? I like the idea of trying to get the organism. If there is a way that it can be done with, as you say, 85 percent success without requiring suture, using the 2 millimeter, that would probably be something to consider.

I think it is reasonable, also, to at least look at susceptibility of the organism. I would assume it would be probably done at reference labs. Obviously, with this kind of procedure, it is only going to be a few places around that are going to routinely do it, but I don't know how much I would require looking at multiple organisms if the natural history of resistance in treponemes is pretty uncommon. I am not sure that doing all the MICs repeat on organisms is going to be very useful.

DR. DATTWYLER: I agree and we don't routinely do that. Our group has published on MICs and time killing curves, and to me, frankly, there is not that much difference between various strains. There is minor

differences.

DR. CRAIG: Dr. Chesney.

DR. CHESNEY: Would it be more or less cost efficient just to do PCRs on all these specimens or to try to culture them and then do PCR on the negative, or do you have any feeling about that?

DR. DATTWYLER: I would do both because there are instances where we have cultured it out, and we have not PCR'd it out, so that there is genetic variability in the organism, so I think that one has to be quite confident of their probes to do that, so I would suggest both.

Again, I should reiterate I would require a genomic probe and a plasmid probe, because the organism has a lot of the important antigens of this organism are plasmid encoded.

DR. CRAIG: Other comments, questions? Anything from the industry? You obviously can submit things later on at another time.

Thank you. We will move on to the next topic then. We will go on to sinusitis.

Dr. Mann will be giving the FDA presentation.

Sinusitis

FDA Presentation

DR. MANN: Thank you, Dr. Craig.

[Slide.]

As an otolaryngologist and as a medical reviewer in the Division, it has been my pleasure to participate in the revision of this guidance document for the acute sinusitis indication.

I would like to start off by emphasizing the fact that this document does cover only acute infections in contrast to the IDSA guidance document of 1992, which covered clinical trials for both the acute and chronic sinusitis indications.

[Slide.]

I think this is an important point to make because there are many differences between acute and chronic sinusitis aside from the obvious differences in length of signs and symptoms.

The clinical presentation of acute sinusitis is fairly typical with nasal obstruction, purulent nasal discharge, and localized pain and tenderness over the affected sinuses, but the clinical picture in chronic sinusitis is often much more vague. Patients will often complain of symptoms such as fatigue, lethargy, vague headaches, and so forth.

With respect to microbiology, acute infections are fairly well characterized by the three major upper respiratory tract pathogens - Strep pneumo, H. flu, and Moraxella, whereas, chronic sinusitis is often polymicrobial in nature and may involve anaerobic organisms and even gram-negative organisms in certain situations.

Finally, while the efficacy of antibiotics has been clearly documented in placebo-controlled trials for acute sinusitis, the role of antibiotics in chronic sinusitis is much less clear. In fact, many of these patients will require surgery as a mainstay of their therapy to correct anatomic abnormality.

The literature also suggests that many of these patients will have a central inflammatory problem rather than an infectious one. For these reasons, and with the unclear role of antibiotic therapy in chronic sinusitis, the IDSA guidelines actually recommend the use of placebo-controlled trials.

[Slide.]

Again, today's document will deal only with acute sinusitis. This document has been presented in its entirety at last year's advisory committee, so I will only be covering areas of the document where we made specific

changes or in response to comments that we received from outside the agency.

[Slide.]

The first modification that we made to the document was a relatively straightforward one. We added fever to the list of possible diagnostic signs and symptoms for acute sinusitis.

A review of the literature demonstrates that probably less than 50 percent of adults with acute sinusitis will present with a fever. However, several studies including one by Williams, et al., demonstrated that fever is probably one of the signs and symptoms, but the greatest specificity in this study was 83 percent although the sensitivity was quite low.

Fever was included in the IDSA document, and we have included it in this document, as well.

[Slide.]

The original draft document specified that allergic rhinitis patients should be identified at baseline, so that they may be analyzed separately, and we feel this is important because allergic rhinitis patients may actually end up having different clinical response rates due to the underlying mucosal inflammation related to their allergies.

We recognized that it may be quite difficult to distinguish between allergic and infectious symptoms. There is a significant degree of overlap in terms of nasal congestion, sneezing, cough.

So, what we are recommending in the revised document is that investigators should document baseline allergy related symptomology during the two week period prior to the onset of sinusitis in allergy patients. Hopefully, this will help us to sort out baseline allergic symptoms from symptoms associated with the infection.

[Slide.]

Also, with respect to inclusion criteria, we received a comment that it is not clear why the Division recommends that patients with acute sinusitis have a history of signs and symptoms for longer than seven days.

[Slide.]

Our reasoning behind this recommendation is nicely summarized in the published proceedings of a recent meeting regarding sinusitis, in which they cited anywhere from between 0.5 percent to 2.5 percent of adult patients with viral URIs will ultimately develop an acute bacterial sinusitis. They go on to say that persistence of the URI for more than 7 to 10 days usually associated with viral

infection indicates the development of sinusitis.

So, by recommending that patients have signs and symptoms for at least 7 days, we are hoping to minimize the inclusion of patients with a viral URI in the study population.

[Slide.]

The original draft document stated that radiographic documentation should include either roentgenography, i.e., plain sinus films, or CT or ultrasound of the affected sinuses and should comment about sinus abnormalities such as mucosal thickening, air fluid levels, and so forth.

We continue to maintain that all three of these modalities, CT scan, plain films, and ultrasound are acceptable means of radiographic documentation of sinusitis.

[Slide.]

However, review of the literature over the past 5 to 10 years reveals a significant change in opinion as to the value of plain films versus CT scan, and specifically, CT scan is now generally thought to be a more sensitive indicator of the mucosal abnormalities associated with the sinusitis.

[Slide.]

In fact, upon reviewing all of the available clinical data, the International Rhinosinusitis Advisory Board last year stated that discordance between plain x-rays and CT scans in detecting sinus abnormality has ranged between 13 and all the way up to 75 percent with conventional x-rays underestimating the presence and extent of the sinus abnormality.

They concluded that CT results are currently regarded as the gold standard for diagnosing sinus abnormality for most infectious processes.

[Slide.]

So, we have revised the guidance document to state that CT scan is the preferred imaging technique when available, recognizing the fact that it will not be available to all investigators in all sites, and it may not be practical, but more important than this even is that whatever modality is chosen, either CT, ultrasound, or plain films, that the pre- and post-imaging modalities should be the same to facilitate a meaningful pre/post-imaging comparison as a measure of response to therapy.

[Slide.]

The original guidance document states that microbiological diagnosis of acute sinusitis is based on

isolating a bacterial pathogen from an antral puncture at baseline.

[Slide.]

We received a number of comments regarding difficulties associated with the antral puncture procedure. Specifically, we received a comment that we may be introducing a possible selection bias by the investigators who would favor the more severe infections, the thinking being that investigators would be less likely to subject a patient with lesser degrees of symptoms to a potentially uncomfortable procedure.

We recognize that this may, in fact, be occurring to some degree in the clinical trials, however, we would maintain that the clinical protocols for acute sinusitis by their nature have rather rigorous inclusion and exclusion criteria, so that we clearly identify a population of patients who have sinusitis. This in and of itself may result in some bias towards more affected patients.

This probably isn't a bad thing since if a drug can be shown to be efficacious in a more severe infection, it will likely be efficacious in lesser degrees of infection, as well.

[Slide.]

We received a comment that there may, in fact, be a possible therapeutic effect from the actual sinus puncture procedure, and this kind of echoes the discussion that we had yesterday with respect to tympanocentesis in acute otitis media, and we do recognize that it would make sense that evacuation of pus from a closed space and irrigation with saline would have some degree of a beneficial effect, but we would maintain that this effect, whatever it is, would be evenly distributed across treatment arms, and in all likelihood a large percentage of patients would have a residual mucosal infection, mucosal edema, inflammation, which would benefit from antibiotic therapy. But this is an interesting point, and it is unfortunate that we don't have actual clinical trials evaluating the therapeutic effect of antral lavage in and of itself.

[Slide.]

Finally, we received numerous comments again kind of echoing the problems with tympanocentesis in acute otitis media, about the difficulty recruiting patients to undergo the procedure, and we do recognize that this, even in the best of hands, can be an uncomfortable procedure for patients to undergo, but at present it remains the only acceptable means of bacteriological identification that we

have available.

[Slide.]

So, of course, we received numerous questions again regarding the value of endoscopically-directed cultures of the middle meatus, whether or not they would be an acceptable means of documenting microbiological diagnosis of acute sinusitis.

This interesting question was discussed in great detail during the last advisory committee meeting, and a very insightful discussion led by Dr. Gwaltney, and unfortunately, not a lot of new information has surfaced since that meeting in terms of our knowledge of the value in this procedure and evaluating bacteriological etiology.

[Slide.]

One of the few pieces of information that we have is a published abstract from the 35th ICAC meeting, which looked at 47 evaluable patients with acute maxillary sinusitis, and these patients underwent both an antral puncture and an endoscopic culture of the middle meatus.

Using as a standard all isolates from the antral puncture regardless of colony counts, there was an overall sensitivity and specificity of the endoscopic cultures of 65 and 40 percent respectively, so not great, but when they

looked at the smaller subset of patients with the three major upper respiratory tract pathogens - Strep pneumo, H. flu, and Moraxella, they noted some better performance with the specificity and sensitivity rising to the 70 to 80 percent range.

One concerning finding that did surface during the study was an increased isolation of staphylococcal species with the endoscopic cultures, raising concerns that there may have been contamination of the endoscopic specimens with nasal secretion flora.

[Slide.]

This concern was also raised in an article by Klossek, et al., in 1996. They performed an interesting study of 139 normal, healthy subjects with no evidence of sinus symptoms at all, and did endoscopic cultures, and over 80 percent of these patients cultured positively, yielding a total of 189 isolates, the major isolates being staphylococcal species, there were 74 coagulase negative staph, 19 Staph aureus.

There was a significant number of Corynebacteria, but relatively few isolates of the common pathogens, only two H. flu isolates and two Strep pneumo isolates, so again raising the concern with possible contamination of any

specimen obtained from the middle meatus with the staphylococci.

[Slide.]

So, based on all of the available studies that we have in acute sinusitis with this technique, the revised guidance document reads that endoscopically guided cultures are not a currently acceptable means of establishing microbiological diagnosis because they may be contaminated by nasal cavity flora, particularly the staph species, and further studies are required to define the role of this procedure in clinical trials, and we eagerly await the results of those studies.

[Slide.]

The guidance document states that, among other things, that the documentation should include quantitative bacterial cultures.

[Slide.]

We received a number of comments regarding difficulties associated with quantitative bacterial cultures, namely, that there is no standard methodology at present for the measurement of bacterial density in sinus aspirate fluid. There is lack of adequate breakpoints for CFU/mL, and that there is just general difficulty in dealing

with the viscous secretions which are often obtained from maxillary sinus aspirates.

We do recognize that these are certainly limitations, difficulties associated with the procedure, but at present this is the best tool that we have available to sort out the issue of specimen contamination versus actual pathogenicity in the infection.

[Slide.]

We did receive a comment that sinuses are normally sterile, and recovery of any of the relevant pathogens should be considered significant regardless of the colony counts, and here we must apologize for some of the confusing terminology in the original draft guidance document.

We do concede that an isolate of H. flu, Strep pneumo, and Moraxella in all likelihood does represent a pathogen from an antral puncture specimen, however, we continue to have concerns about staphylococcal isolates and the possible contamination from the actual procedure.

[Slide.]

So, we have revised the guidance document to state that isolation of the common pathogens, Strep pneumo, H. flu, and Moraxella from a maxillary sinus aspirate is considered significant independent of colony count, however,

with Staphylococcus aureus we will consider it an etiologic agent only when isolated in pure culture with bacterial counts greater than 10^4 CFU/mL.

[Slide.]

We received comments regarding the statement in the inclusion criteria that pathogens should be susceptible to the study and control drugs. We received numerous comments that this runs counter to trials designed to assess empirical or real world therapy, and that it would interfere with our assessment of outcome in patients with resistant strains. This issue has actually been touched on in some of the other indications.

[Slide.]

I will merely state that we do concur with these comments, and we have revised the guidance document to state that pathogens should be susceptible to the study and control drugs, however, should the patient show clinical improvement, despite the isolation of the non-susceptible organism by in-vitro testing, that the investigator may elect to continue treatment with the study drug and to collect all protocol-specified data.

[Slide.]

Finally, the last change that we made to the

document was under the Clinical Outcome Section, and regarding the requirements for clinical cure, the original document stated that we expected to see at least improvement in the radiographic appearance of the sinuses.

We have now, in recognition of the fact that the radiographic improvement often lags behind clinical improvement, we have changed this requirement to read that at least no worsening in the radiographic appearance of the sinuses be noted.

[Slide.]

So, to quickly summarize the changes that we have made to the document, include the addition of fever to the list of possible diagnostic signs and symptoms consistent with acute sinusitis. We recommend that investigators should document in the CRF baseline allergy-related symptoms for the two weeks preceding acute sinusitis in allergic rhinitis patients.

We recommend that CT scan is the preferred imaging modality to support the diagnosis of acute sinusitis, but still maintain that plain sinus films and ultrasound are acceptable means of documenting radiographic appearance in sinusitis.

[Slide.]

However, whatever imaging study is chosen, the pre- and the post-treatment imaging modalities should be the same.

With respect to sinus endoscopy, these endoscopically guided cultures are not currently an acceptable means of establishing microbiological diagnosis. We have no published studies comparing a head-on well-performed antral puncture with endoscopically guided cultures in acute sinusitis, and there is the concern regarding staphylococcal contamination of specimens.

With respect to direct antral puncture, isolation of Strep pneumo, H. flu, and Moraxella will be considered significant independent of colony count.

[Slide.]

However, Staph aureus will be considered an etiologic agent only when isolated in pure culture with counts greater than 10^4 CFU/mL.

Investigators may elect to continue study drug treatment in patients showing clinical improvement despite the isolation of a resistant organism by in-vitro testing.

Finally, with respect to clinical cure, we expect to see no worsening in the radiographic appearance of the sinuses.

This concludes my presentation.

Committee Discussion

DR. CRAIG: Thank you very much. Questions? Dr. Henry.

DR. HENRY: Actually, I had three questions or comments. The first is, is it more acceptable to patients to have an endoscopic procedure done to obtain culture specimens than it is an antral puncture?

DR. MANN: By far, I think patients would tolerate an endoscopic procedure much more readily than they would an antral puncture. With antral puncture, you have to do a local injection of anesthetic. There is a lot of pressure involved with getting the trochar into the actual sinus itself, which is often uncomfortable even with the best of local anesthesia.

The endoscopic technique is much quicker and easier on the patient, but we have concerns about it.

DR. HENRY: So, if you want specimen for culture, and you now have a classic study from '96 which tells you basically what some of the normal flora is--because these were healthy patients, so you really didn't see Strep pneumo or Haemophilus or Moraxella, so why not ignore the coag-negative staph, Corynebacterium, and Propionibacterium,

and Staph aureus can be tough because 30 percent of people are nasal carriers, but if you focus on the big 3, the same ones you were going to focus on for the sinus antral aspirate, I mean why not allow an endoscopic procedure, disallow those organisms you know are likely contaminants because you will have better compliance in terms of getting culture data.

When you talk about colony counts of Staph aureus, you just got done saying it is hard to do quantitative cultures, so how can you even have a cutoff of Staph aureus greater than 10^4 in pure culture?

I mean Staph aureus to me seems like it is going to be the hard one to interpret, but an endoscopically obtained specimen for Strep pneumo, Haemophilus, and Moraxella, it seems a better bet in terms of getting the material and getting the pathogens you are looking for.

So, I don't know that I would be so strict and disallow it.

DR. MANN: I think those are very good points.

DR. CRAIG: Do you know what the colonization is in people with viral URIs, because that is the population that starts off and then develops sinusitis, not perfectly normal, healthy volunteers.

So, I would like to know what the microbiology at least looking from the study that was done where they had both taps and had done the other, the specificity, I thought was relatively low, 40 percent.

DR. MANN: That is a good point, and I guess one of my major concerns is the fact that all we have is an abstract. We have no published data on this at all, and while the abstract does sound promising, if you can focus down onto the three major pathogens, we haven't even seen the data yet. We have no published data whatsoever actually looking at these isolates. I think it is just a little premature at this point without any published data.

DR. ALBRECHT: I am trying to recall from the last advisory committee when Dr. Gwaltney presented this topic, I believe he or someone brought up the other consideration that has been mentioned of what about nasopharyngeal cultures to predict what is in the sinus.

In the studies where that was done, there was a discordance or incomplete concordance or whatever, and I think probably the same kind of reservation was either brought up or implied about the endoscopy, that you may get an H. flu, but you don't know where that came from, whether it really just came from near the nares or whether it truly

was within the sinus, much the issue, of course, that Dr. Craig raised.

DR. MANN: Especially in somebody with the signs and symptoms of acute sinusitis blowing their nose, you know, snorting secretions and stuff that can really confuse the picture.

DR. CRAIG: Dr. Norden.

DR. NORDEN: I wasn't clear. Were you saying that patients have to have a history of seven days? I saw the industry comment, but I wasn't clear. Is that part of the guidelines?

DR. MANN: Yes, signs and symptoms for seven days.

DR. NORDEN: I think that may help you to exclude people with viral infection first, but I am not convinced that some patients with bacterial sinusitis have symptoms for that long. We have certainly seen patients--and I can speak from personal experience--of having symptoms for no more than two days and a pure culture of pneumococcus isolated on puncture.

DR. MANN: Certainly if it is odontogenic in origin, as well, that will show up a lot quicker than a viral, but there is quite a bit of difficulty in sorting out a viral picture from a sinusitis picture both on clinical

grounds and on radiographic grounds very early on in the infection, and this is the best technique that we have kind of come up with in terms of trying to increase the specificity for the disease for the patient population.

DR. MURRAY: Do these symptoms include typical sinusitis symptoms for more than a week or the symptom complex of an upper respiratory type symptoms?

DR. MANN: I think just general symptoms of nasal congestion, rhinorrhea, would be for a period of over a week as cited in the literature references is a good indicator that bacterial sinusitis is developing, so I think not necessarily specifically sinus pain and tenderness, but the whole complex of nasal secretions, nasal congestion for at least seven days of documentation from a radiograph would be considered.

DR. CRAIG: In the situations where you don't do the puncture, I mean clearly I remember from the discussion we had before when Dr. Gwaltney was here, that in order to increase the sensitivity, that you were dealing with bacterial sinusitis about two-thirds of the time I think he said or around 70 percent of the time, you needed, you know that was the characteristic, but if you started looking earlier, then the frequency at which these were true

bacterial infections dropped down, so you are looking at more and more viral sinusitis when you started looking at earlier time periods, therefore, going out for a longer period of time.

Now, it may be that in the puncture studies, one wouldn't have to be as tight, but I think what the companies are going to do, doing a lot of punctures where they are not going to grow organisms out.

Again, it is probably to their advantage to try and look a little bit later when it is much more likely that it is going to be bacterial infection than it is going to be viral infection.

Dr. Chesney.

DR. CHESNEY: This seems to exclude frontal sinusitis in that you mentioned antral punctures, but we have seen a number of adolescents who present very acutely, much faster than the 7 to 10 days, with very bad frontal sinusitis, and you have a surgical specimen to culture. Can they be included or are you just dealing with maxillary sinusitis?

DR. MANN: The guidance document covers sinusitis as a general clinical entity which would include ethmoid sinusitis, frontal sinusitis, and maxillary sinusitis.

Obviously, there is the potential that a patient would have a negative puncture if they had just isolated involvement of the frontal sinuses or the ethmoid sinuses, but with well documented radiographic evidence of frontal sinusitis, purulent nasal discharge, and symptoms to go along with it, I think they would certainly be included.

DR. CHESNEY: Does it include mastoiditis also or just paranasal sinuses, this protocol?

DR. MANN: It includes all, maxillary, frontal, ethmoid, and sphenoid.

DR. CHESNEY: And mastoid?

DR. MANN: Mastoid is not considered a paranasal sinus.

DR. CRAIG: I think the reason why most of this is maxillary sinus, I mean if in those areas where you can get a specimen, and know what you are dealing with on sites outside the maxillary sinus, it is probably perfectly fine.

What we don't know is what is the natural history of the other kind of infections where you don't get a culture, what percentage of those are viral, what percentage of those are truly bacterial, so it is much harder in the study that one does when one doesn't do the puncture to include those patients because the natural history of those

other sites has never really been studied, maxillary sinusitis is the one thing that has been very well studied, but I would hope that if one punctured it, or had a good specimen, they cultured out the organism, that those other sites could be used in the study that usually uses puncture.

DR. MANN: That is correct.

DR. CHESNEY: Does this also include children who might have a positive blood culture, and that would be considered acceptable if you had ethmoid clouding?

DR. MANN: Certainly, there would be difficulty in obtaining a sinus aspirate in a child to document infection just because the sinuses are quite small, and the problems with hitting tooth roots, and so forth, when you are doing antral puncture in a small child is problematic, but I think probably provisions could be made just based on signs and symptoms, purulent nasal discharge for more than seven days, common symptoms associated with sinusitis that they could be included.

DR. CRAIG: You would probably get very, very few, if any.

DR. ALBRECHT: That is correct. We have not seen actual clinical studies, many clinical studies done in children with sinusitis. The exception is some recent

submissions where actually Ellen Wald did do some studies in some of the recent antimicrobials, and actually, that allows me to lead into the comment that as far as the seven days of symptoms, when we had an advisory committee--this was '93--and we invited her.

Her belief was that in children, you should have signs and symptoms of URI evolving into sinusitis of at least 10 days duration. I said, "You mean nine days wouldn't do it?" She said, "Ten days." So, I think in those settings if we didn't have the microbiology, but we had the 10 days, I think we would believe that.

DR. CRAIG: Dr. Soper.

DR. SOPER: So, the inclusion criteria is seven days of symptoms and radiologic evidence of sinusitis, and then the issue is how do you isolate a microorganism that you can determine susceptibility to the new antimicrobial that you are testing.

It sounds to me that even with antral puncture, that you are going to get a lot of background that is not going to be particularly meaningful because you are going to focus on the three major microorganisms that you have already discussed including the possibility of Staph aureus.

Nobody is going to do antral punctures is what I

am hearing, endoscopy is much easier. Why don't you do endoscopy, limit and even selectively culture for those three microorganisms, do a Gram stain. If it is positive, do a quantitative culture for Staph aureus. Limit your microorganisms to the four microorganisms that I just mentioned, and that is probably as good as you can do.

DR. MANN: Again, we really lack the documentation in the literature as to the value of this as a tool to obtain a microbiological diagnosis. We have no published data whatsoever. The abstract certainly is promising in the sense that when they hone down on the three major respiratory pathogens, that the sensitivity and specificity seem to go up.

But with respect to antral punctures, the results from those are considered quite reliable, even Staph aureus, as long as it meets the criteria that we have in terms of greater than or equal to 10^4 CFU/mL.

Until we have better data regarding head-on comparison of a well-performed antral puncture with the endoscopic technique, I think it is premature to recommend that as a tool to use.

DR. SOPER: So, is industry doing the antral punctures?

DR. MANN: Yes.

DR. ALBRECHT: Definitely, the agency is interested in finding techniques that might be acceptable, but I think Dr. Gwaltney very elegantly summarized sort of the limitations of using endoscopy given the methods that we have available or at least had available as of '97.

I think we did hear some comments from industry that the endoscopes are becoming more flexible, more sophisticated, tinier, that the contamination along the way may be minimal, and so I think we are encouraged that in the future, perhaps this will be an option, but, in fact, the correlation at least that we had as of last year in the literature, and Dr. Mann has not been able to find anything more recent, suggested that it would not be prudent to abandon the antral puncture technique.

DR. MANN: There are a lot of other unanswered questions like how do you handle a patient who has no sinus drainage into the middle meatus, because their ostium has been swollen shut, how do you standardize the methodology. People might be using suction traps on one end and Calgie swabs on the other, so we have no standardized technique as to how the procedure should be done.

I can tell you personally it is very difficult to

get a Calgie swab or a suction trap up into a sick nose which is very swollen and edematous, and to clearly get into the middle meatus without contaminating the tip. So, there is a lot of problems that have to be confronted and answered.

DR. SOPER: I couldn't agree more. I certainly understand the problem of contaminated specimens if not better than anybody here, but the point is that if the point of the study is not necessarily to define the microbiology of the infection, I mean that is going to require a rigorous antral puncture data, et cetera, but to determine the efficacy of an antibiotic and to try to determine the pathogens that you wanted to have activity against, you can be less rigorous in the microbiologic aspect.

If it is going to mean that industry or that investigators are not going to do antral punctures, there are ways of getting around that. If they are willing to do the gold standard, that is great.

DR. CRAIG: Any other comments?

Thank you, Dr. Mann. Now we will take our break. It will be 15 minutes. We will start again at 3:15.

[Recess.]

DR. CRAIG: The next topic is acute exacerbations

of chronic bronchitis and secondary bacterial infections of acute bronchitis. The FDA presentation will be by David Bostwick.

Acute Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis

FDA Presentation

DR. BOSTWICK: Good afternoon.

[Slide.]

My name is David Bostwick. I am a clinical reviewer in the Division of Anti-Infective Drug Products.

This presentation is on bronchitis. It was written by Dr. Susan Thompson who can't be with us today, so I will be making the presentation for her. Since I didn't write it, it has the great virtue of being the shortest presentation you will see today.

[Slide.]

This is just for definitions. Bronchitis has been split into two entities, acute exacerbation of chronic bronchitis, which we will refer to as AECB, and secondary bacterial infection of acute bronchitis, which we will refer to SBIAB.

[Slide.]

This is a little bit of regulatory history. This

indication years ago was granted as lower respiratory tract infections, and it included pneumonia and bronchitis. The guidance currently has split bronchitis into two separate subcategories, SBIAB and AECB. There are also two subcategories for pneumonia which we won't discuss.

In the IDSA guidelines, which were generated in the early 1990s, there is an indication for AECB, but SBIAB is not included.

In the current guidance, we have separate indications for AECB and SBIAB although the SBIAB guidance currently notes the benefit of antimicrobial therapy is unproven for SBIAB.

[Slide.]

A little more regulatory history. This subject was discussed in October 1992 by this committee. Concerns were raised regarding the validity of SBIAB during a discussion of the Points to Consider document, and it was also discussed last year, March of '97.

There was a presentation of the Guidance to Industry document which included both AECB and SBIAB, and there was discussion of the validity of the entity of SBIAB as an indication to be granted by the Division.

[Slide.]

Some of the points that were discussed during that March '97 committee meeting. There is no data showing benefit of antibiotic treatment of SBAIB, and we will discuss that a little more later here.

Use of antibiotics for this entity would perpetuate the overuse of antibiotics by encouraging continued comparative trials with implications regarding resistance and economics.

There was also discussion in designing such trials of using placebo-controlled trials with microbiological documentation.

[Slide.]

Since the March '97 meeting, we have had some minor comments on AECB with no major changes recommended, so we won't be discussing that any further here. Dr. Craig does have some comments on AECB which he will speak to after this presentation.

We would now like to consider whether SBIAB is appropriate for the Agency to grant as an indication for antimicrobial therapy.

[Slide.]

Some background on SBIAB. As you all know, bronchitis has multiple causes including infection,

allergies, and environmental exposure. It is believed that infectious acute bronchitis is primarily viral in origin. Some of the causative agents, influenza A and B, parainfluenzae, rhinovirus, et cetera, and it often occurs in otherwise young, healthy adults.

[Slide.]

This slide concerns the possible microorganisms that might be associated with SBIAB. We find that there is sparse support for a role in either acute bronchitis or SBIAB for S. pneumoniae, H. influenzae, S. aureus, or M. catarrhalis.

As far as Mycoplasma and Chlamydia, the role in bronchitis as far as we can tell is poorly defined. It may cause acute bronchitis probably in less than 10 percent of cases.

[Slide.]

SBIAB is rare and occurs in specialized circumstances. These are in neonates in connection with tracheostomy and immunocompromised hosts, and is a superinfection after an influenza infection.

[Slide.]

There is a review paper which is written by Dr. MacKay, in the Journal of General Internal Medicine, which

concerns the use of antibiotics in patients with acute bronchitis. It is really a review of the literature. He found nine randomized, double-blind trials comparing antibiotics with placebo and/or bronchodilators in patients with acute bronchitis in the time period 1966 to 1995.

A successful outcome in these papers was defined as symptom resolution, resolution of cough or fever, and return to work or normal function.

[Slide.]

None of the nine studies reviewed by Dr. MacKay found an overall significant benefit of antibiotics. Two studies did show albuterol to be more effective than a placebo or antibiotic.

The conclusion he drew was that antibiotics offer no benefit to patients with acute bronchitis.

[Slide.]

We do have some SBIAB trials. Several studies have demonstrated that antibiotics will effectively eliminate S. pneumoniae and H. influenzae, but they were not placebo controlled and they were confounded by the possible nasopharyngeal colonization. We don't have any controlled studies is basically what we are saying here.

[Slide.]

We do have data from the National Center for Health Statistics at CDC. There are 16 million prescriptions per year for bronchitis, AECB and SBIAB combined, and 80 percent of these are felt to be unnecessary. These bring up obvious problems certainly. It would appear this overuse would contribute to resistance. There are economic considerations in prescribing drugs for diseases for which they have no use for.

[Slide.]

Our conclusions. Acute infectious bronchitis is usually a viral infection. Antibiotic administration offers no benefit to patients with acute bronchitis. Secondary bacterial infection of acute bronchitis is a very uncommon clinical entity if indeed it occurs at all.

[Slide.]

The question we have for the committee is: Is secondary bacterial infection of acute bronchitis a disease entity for which antibacterial therapy should be studied in clinical trials?

I am far from an expert in this subject. Luckily for all of us, Dr. Craig is, and many of my colleagues are, so I will sit down and let the discussion proceed.

Thank you.

DR. CRAIG: I will take that one on very easily and say no.

Committee Presentation

DR. CRAIG: I think at least from the trials that are published, that I have been able to look at, even those where they followed symptoms over time, the curves in terms of disappearance of symptoms are essentially superimposable, so it is even hard to show that antibiotics speed up the natural response to this disease.

In this era of increasing resistance, there have been other people besides myself, editorials that have been written in journals clearly stating that this is a disease that we should not be giving antibiotics to, antibiotics do not benefit people. All we are essentially doing is subjecting them to the potential of side effects and contributing to the emergence of resistance.

So, to me, I would need a lot of good theory that something would help. Now, it doesn't mean that something that is anti-inflammatory might not help and speed up the response, but an antibiotic that is specifically driven to just try and eliminate the organism, I think there is enough data out there to suggest that those kind of trials would not be helpful, but if somebody has a compound that was

anti-inflammatory, that was going to speed up the disease and want to do a placebo-controlled trial, that is fine, but not an antibiotic.

Any disagreement from my colleagues on the committee here?

Committee Discussion

DR. RELLER: No.

DR. CRAIG: You are not shaking your head one way or the other, Barth. I never know.

DR. RELLER: When I went through this, and answered all these questions, I had no, no, and no-no-no.

DR. CRAIG: In that same respect, though I do have some comments about acute exacerbations. I think what we are learning now from the placebo-controlled trials that were done in this disease, that people have been interested in trying to find out what characteristics identify those patients that are going to see a clear benefit from antibiotic therapy and also to identify those patients that do not see or do not get a benefit from antibiotic therapy.

What has come out of these studies is three primary symptoms that tend to be associated with getting a benefit from antibiotics. The three are increased volume of sputum, increased purulence of the sputum, and increased

dyspnea.

If we look specifically at the criteria that are listed here, one has in the guidelines, cough is in there, and cough has not been one of the factors that has been associated with increasing the chance that antibiotics will be beneficial.

You do have increased sputum production and increased dyspnea, but you do not have increased purulence. If you have all three of those, essentially what you refer to as having a Type 1 exacerbation, if you have only two of the three, you have a Type 2 exacerbation, and if you only have one of the three, you have a Type 3.

If you look specifically at those situations in which antibiotics clearly are beneficial, it is clearly in the Type 1, where you have all three, and those that have Type 2 exacerbation, it may be beneficial, but the data really suggest that for those that only have one of those three items, the antibiotic is not beneficial.

So, again, I would recommend that we at least make sure that patients have two out of the three, but they should be encouraged to try and enter patients that have all three of these criteria, but specifically that they not enter patients that only have one of those three criteria.

So, I would want to see at least two, but encouraging to have a significant number of the patients actually have all three.

Comments?

DR. NORDEN: That is very interesting. Where is that data found?

DR. CRAIG: There has been a couple of publications on this. Also, Ball from Scotland has been looking at this. I have talked to several of the people like Tom File, that had been working a lot in these kind of trials, and I think at least among the academic community, there is an increasing appreciation that yes, we can identify those patients that stand a better chance of benefitting from the antibiotic and being able to exclude those that may not benefit at all from the antibiotics from clinical trials.

In that way, try and make sure that the use of drugs in exacerbations also starts to be more realistic, so we use it in those people where it is going to have a benefit, and not use it in those that don't.

So, there is a literature that one can put together that the industry could cite for these criteria.

Any other comments?

DR. PIERCE: Phil Pierce from Bristol Myers Squibb. Can we extend our comments beyond that? Are you ready for that?

DR. CRAIG: Sure.

DR. PIERCE: I think those were Anthony [Neissen's] criteria we used from the Canadian literature.

DR. CRAIG: You are right.

DR. PIERCE: One thing I would like to tease out a little more, and it can come up later in a discussion of Gram stain, is the inclusion criteria of 25 WBCs and less than 10 EPIs.

I have absolutely no problem with the 25 WBCs, and that includes people with the disease, but people with greater than 10 EPIs and greater than 25, also have an exacerbation of AECB. The FDA and other approvals has discarded, if you will, allowed people with greater than 10 EPIs into bronchitis studies.

So, I would like to know as to whether that criteria would be relaxed for this guideline or what is the rationale for maintaining it. Is that clear?

DR. CRAIG: I understand what you are saying. It is usually, you know, it's the ones that have 15, 20, those are the numbers that you occasionally find, and in my own

mind, I agree with you, if you look around on that slide, oftentimes you can find areas where it meets the criteria, but if you are trying to count the whole slide, you do find that it may not reach it.

I don't know if Barth wants to comment now or just say that that is something we will touch on later when we are talking specifically about the Gram stain.

I think what we tend to on focus here is primarily that this is a clinical diagnosis. We have tended to say we are not going to really be looking at the microbiology, and so my feeling is I would try and tighten up the clinical to make sure that we are looking at those patients where the antibiotic is going to be beneficial, make sure that obviously if we are talking about increased purulence of the sputum, and that is an indication which is not there right now, and that one is added, that that is an indication coming in, I think, first of all, you may find that that may not be as big of a problem, but I would be less concerned about the situation where there are a lot of polys and you have a few more epithelial cells than the situation where obviously you don't have many polys. Those are clearly contaminants.

I could see loosening for it by tightening up the

clinical aspects.

DR. PIERCE: Thank you.

DR. ALTAIE: I would just like to add that this whole issue will be discussed in a talk that follows, the nosocomial pneumonia.

DR. CRAIG: Dr. Reller.

DR. RELLER: Recognizing that there will be further discussion later, to me, the answer to this question hinges on how important the committee, the agency, the investigators feel that delineating an etiologic agent is--I mean that is the purpose of grading sputum specimens, to enhance the reliability of the cultures.

If the cultures are not important, and in my view, from a clinical standpoint they are not, that is, it is a clinical diagnosis with an exclusion of pneumonia where the cultures I think are still important with the chest radiograph.

In other words, the patient who has the clinical syndrome with the parameters that you describe that are associated with the possibility of a response to antimicrobial therapy, with a chest x-ray that does not corroborate the presence of a complicating pneumonia, then, it is the clinical entity and the response thereto that is

important, and not what the organism is in the sputum, the bacteriology which has been well characterized.

Now, if someone is coming in and trying to get a claim for acute exacerbations of chronic bronchitis owing to Staphylococcus epidermidis like some things have been with pneumonia owing to this agent, then, I think we must have sputum criteria in there to keep some semblance of science in the whole process.

So, I think that the answer cannot be made in the isolation of how important the microbiological data is in the evaluation of response to antimicrobial agent for this indication.

DR. SOPER: It seems to me that the evaluation of sputum to confirm this increase in purulence is important regardless of whether the sputum is sent for culture. The question I would have is, is there any utility in reevaluating sputum for then the absence of purulence after the completion of therapy.

In other words, if you have a chronic bronchitis and you have no polys in your sputum as a result of chronic bronchitis, but you get an acute exacerbation and your sputum increases in its volume and you develop polys, does it then go away with antimicrobial therapy?

DR. CRAIG: I would have to look at a lot of things, but clearly the purulence drops, but the question of how far it drops in terms of the number of white cells that one sees on a preparation, I would bet that you could still find pockets in which you could still find some of the material, white cells, but it doesn't completely disappear.

DR. STAGER: Bill Stager, HMR. Would you recommend sizing a trial strictly based on a clinical outcome, or would you suggest that for future purposes, it would be best to size for also microbiological outcome given the current state?

DR. CRAIG: I guess my question would be what is going to happen with resistant organisms in that issue. That is the only reason that I would think about the organism. Outside of that, it would be mostly for clinical reasons, but I will let the FDA respond.

DR. ALBRECHT: Actually, on the topic of whether to size it based on clinical or the micro endpoint, and it goes to the issue of how we approve antimicrobials, which is stating the indication and then listing the pathogens where efficacy has been demonstrated, if we go into the current proposed guidance, we talk about conducting one statistically adequate and well-controlled trial in which

both the clinical and the microbiological components of the disease are documented in the patient, and then go on to recommend a second trial.

If the drug isn't also being looked at in pneumonia or related infection, but simply an acute exacerbation of chronic bronchitis, we go on to recommend a second trial where a clinical endpoint is of primary interest and where although the suggestion is made that microbiology should be pursued, that is not looked at as a critical component.

So, I think in the context of those recommendations, I think perhaps the first comment, are those recommendations reasonable or is there comment on that, and second, back to Dr. Reller's comments, would that imply that only when we are specifically looking for microbiologic diagnosis we should use Gram stain at baseline.

DR. RELLER: We just strongly recommended not having the secondary bacterial infections of acute bronchitis, because the clinical and microbiological etiologic things didn't fit together to support that.

Is it time to look at this entity very carefully based on the available data and the pathophysiology? I

strongly support at least two and maybe even three criteria, I mean there are plenty of patients out there, in accord with the comments that Bill has made.

As the document currently stands, there is an assessment after therapy of eradication of the pathogen present before, but the nature, as best as I think it's understood, the pathophysiology is that these patients by definition have a respiratory tract that is colonized with usual respiratory flora and including the ones that are associated with their exacerbations that respond to antimicrobial therapy when the dyspnea, the increased purulence, and amount of sputum is present.

The organisms are still there, are expected to be there. They may be harder to demonstrate because the volume of sputum is reduced, and its purulence is reduced with effective therapy, and they breathe better, and they even have improvement in the measured mechanics with control of the acute exacerbation, but the secretions from below the larynx are not sterile, and one wouldn't necessarily expect to eradicate the putative pathogen.

So, to require an eradication of something that you expect to be there does not deny its role, that it is just that that becomes an inappropriate endpoint, and

clearly could not be fairly assessed unless one had a quality sputum in the beginning and a quality one in the end, and it seems to me we may be better off in recognizing the pathophysiology and putting the emphasis on very stringent clinical criteria, and then a response that does not include the microbiology at all.

We have talked about the microbiology driven, the microbiology and clinically driven, and the clinically driven, and I think this is, and should be, a clinically driven entity.

Bill, what do you think?

DR. CRAIG: I am not ruling out microbiology from the point of view is that our previous studies have essentially been a mixture of patients, those in which the antibiotic may be important and those in which the antibiotic may not have had any role at all.

If one was able to look at it just in those patients where the antibiotic was important, there might be some differences that one could see. It's a question that I think is open, but I agree with where we are right now without that bit of information. This clearly needs to be one that is driven on clinical means until we get that additional information.

DR. GOLDBERGER: It's conceivable that if a company were simultaneously, which is common, pursuing, for instance, a community-acquired pneumonia claim and got adequate microbiology from there, since we would expect a lot of overlap, and were using the same dosing regimen, both amount of dose and duration, that microbiology might not be very important in this particular indication since one would like to believe if the drug were effective and confirmed pneumonia, and were used in exactly the same way, in ABCB, it ought to work as well. In that case, that might also lend itself to focusing more on the stringent clinical criteria.

That is an issue we would probably want to talk about a little more, but it seems conceptually possible. As a practical matter, on more than one occasion, the dose for this indication turns out to be either shorter or lower, and that might influence being able to do that.

DR. CRAIG: Yes, Dr. Dattwyler.

DR. DATTWYLER: I think that we sometimes forget that antimicrobials have other effects. These antimicrobials can have anti-inflammatory effects or effects on the bronchial secretions, so I think that just looking at microbiologic criteria may not be adequate, and I agree with

you that clinical criteria, especially with those parameters factored in, have to be the mainstay.

DR. CRAIG: Dr. Chesney.

DR. CHESNEY: This not being a pediatric disease, I wonder is there any correlation between what you isolate and the antibiotics, and specifically if you have resistant pneumococci, and you use an antibiotic to which the pneumococci are resistant, do you still see improvement, because I know in cystic fibrosis, you often do get an improvement, which may be due to the nonspecific effect of antibiotics even when the organisms are resistant. You get a decrease in the load, a decrease in sputum production, and so on.

Are there good studies correlating the susceptibility of what you do isolate with the antibiotic?

DR. CRAIG: In fact, some of the studies suggest that you do well even with resistant organisms, but I think again the question is, is what that population was, was that the population where antibiotics aren't going to be beneficial at all, or is it the population that fits the definition where antibiotics tend to help, plus I do agree they clearly macrolide the drugs which have a lot of other effects on secretion, anti-inflammatory effects besides

their antimicrobial effects that could also result in response without having any antimicrobial effect.

DR. RELLER: I think the current understanding of therapy in patients with cystic fibrosis, that they, in fact, are a special case, but are exacerbations that is clinical deteriorations of what is a chronic bronchitis, and that one doesn't necessarily, as has been demonstrated in that population, have to even postulate necessarily that the non-bacterial effects, that one could have an effect short of eradication of the organism that might alter what the bacteria are producing or contributing that secondarily incite some of these other inflammatory things that cause clinical deterioration, ending up in dyspnea and altered gas exchange, and so on.

But it is a question of how can one assess that. In cystic fibrosis, clearly the endpoint is not eradication of the organism, and it may not be here. In trying to fuse these approaches, if the entity were tightened clinically, what I think I heard you say, Bill, is that there may be issues of before and after microbiology that may be more clear if one had a tighter group of patients who were being studied.

DR. CRAIG: Yes, plus I think resistant organisms

also can add to that, because before, with most of the drugs being active against virtually all the organisms, you didn't have those organisms that might not be resistant.

I mean the kind we had before were more with macrolides which can have some other effects, like erythromycin, that can have other effects besides just its antimicrobial effect, and I think with resistant organisms, one has a chance then to see with many current drugs that would be considered as comparative agents, which you may expect wouldn't be active against those organisms, to see if that can also be translated into clinical failure.

So, I think you stand a chance of being able to make a little bit more correlation if you tighten up the clinical group, and now the fact that many pneumococci are resistant with many of the comparative agents that would be used, we would expect there to be failures, and one gets a chance then to see if that is also translated into clinical failures.

DR. RELLER: They, maybe the way out of this is to tighten the clinical criteria since these documents evolve over the years, tighten the clinical criteria, retrain the microbiology, but recognize that persistence of the organism would not preclude clinical success. In other words, sort

of prioritize what the important issue is at the endpoint to enable one to find the answer to the questions that you raise.

If that is the case, then, I would strongly urge to give some reasonable chance at interpreting the microbiology data to retain the grading of sputum to exclude those patients who have their lower pus secretions grossly contaminated with mouth flora being swished around before being put into the cup.

DR. CRAIG: Any other comments, questions?

Hearing none, we will move on then to the next topic, which is community-acquired pneumonia and nosocomial pneumonia. Alma Davidson will give the FDA presentation.

Community-Acquired Pneumonia and Nosocomial Pneumonia

FDA Presentation

DR. DAVIDSON: Good afternoon.

[Slide.]

My name is Alma Davidson. I am a medical officer for the Division of Anti-Infective Drug Products, Office of Drug Evaluation IV.

In the next 20 minutes or so, I am going to talk briefly about some of the highlights of the document on developing antimicrobial drug products for the treatment of

bacterial pneumonia particularly nosocomial pneumonia.

[Slide.]

At the outset let me say some background about this document for the sake of the new members of the committee and for those who were present in 1997 to refresh your memories.

In the advisory committee meeting of March of 1997, some of the issues that we addressed were as follows. First, the separation of community-acquired pneumonia and nosocomial pneumonia into two documents. Secondly, that the criteria for the nosocomial pneumonia be more stringent, and in the nosocomial pneumonia patients to have both fever and leukocytosis plus at least one of the other signs and symptoms.

[Slide.]

The other issues that were addressed and resolved were as follows. The diagnostic criteria for ventilator-associated pneumonia, subsetting patients with ventilator-associated pneumonia, how to handle patients who have evidence of multiple pathogens in their sputum, and that the Gram stain should correlate with culture results.

This issue, including some other issues, will be addressed by Dr. Sousan Altaie, our microbiologist.

[Slide.]

Switching gears, we had questions and comments from industry in 1997. The comment on here is the clarification of the Division's view of the role of blood cultures and susceptibility testing for outpatients with pneumonia. The answer to this is we do not require blood cultures for outpatients with pneumonia, but we do require blood cultures in all hospitalized and pediatric patients. Rather, it is a clinical judgment call by the physician when ordering such laboratory tests.

[Slide.]

The next comments refer to the inclusion criteria, which are eliminating blood cultures as inclusion criteria since these are pending for two days after enrollment; recommend eliminating fever as inclusion criteria since fever is absent from one-third of pneumonia cases, especially in the elderly; recommend eliminating white blood cell count since labs often pending for several hours at time of prestudy visit or are being sent to the central lab.

Our reply to these comments is that all this inclusion criteria really contribute to the overall diagnostic criteria of bacterial pneumonia, hence, the above should be present particularly in nosocomial pneumonia.

[Slide.]

Lastly, for this question of atypical pathogens, are sputum screen and culture required for inclusion criteria? Our answer to this is we still prefer culture of these type of pathogens, however, sputum screen is not necessary. The issue of alternate diagnostic tests, the serology may be used to establish infection with one of these pathogens and should be discussed with the reviewing division prior to initiation of the study.

[Slide.]

The next slide shows the changes in the new document. The separation of community-acquired pneumonia and nosocomial pneumonia. Disease definition and additional text in inclusion and exclusion criteria of community-acquired pneumonia. Clarification of evaluation visits. Dichotomous clinical outcome responses of clinical cure and clinical failure, eliminating the improvement category, and nosocomial pneumonia, its inclusion and exclusion criteria.

[Slide.]

This is nosocomial pneumonia. Any takers on the Gram stain? There is Strep pneumo at the top of the slide, and at the bottom are Haemophilus influenzae, and the bottom

is Pseudomonas aeruginosa.

[Slide.]

Disease definition. Let me start with the disease definition of acute nosocomial bacterial pneumonia, which is broadly defined as a pneumonia characterized by a new cough with auscultatory findings of pneumonia in conjunction with a new infiltrate or progressive infiltrate or infiltrates on chest radiograph, accompanied by fever or hypothermia, leukocytosis, and sputum production, which could be purulent, and caused by polymicrobial organisms.

[Slide.]

Continuing with the disease definition. This is acquired by a patient in the following settings: any hospital or long-term care facility after being admitted for more than 48 hours or less than 7 days after a patient is discharged from the hospital with the caveat that the patient's initial hospitalization will be greater than or equal to 3 days duration.

[Slide.]

The risk factors associated with the development of nosocomial pneumonia are the following: host factors, such as inpatients with extremes of age, patients with severe underlying disease including immunosuppression.

Factors that enhance colonization of the oropharynx, the trachea, and upper gastrointestinal tract by gram-negative microorganisms, for example, administration of antimicrobials, intensive care unit admission, and others are factors that favor aspiration or reflux, such as endotracheal intubation, and insertion of nasogastric tube, prolonged use of mechanical ventilation with potential exposure to contaminated equipment, as well as contaminated or colonized tents of the health care personnel. Lastly, factors that impede adequate pulmonary toilet, such as in prolonged thoracoabdominal surgeries, and even supine position.

[Slide.]

Before I go any further, let me say some of the problems and difficulties associated with the diagnosis of nosocomial pneumonia, and to mention a few are the following. For one, the clinical criteria lack specificity. There are no gold standards for diagnostic procedures, for example, in basic procedures.

There is high potential for more than one ongoing infectious process in the intensive care unit, thereby relying on positive culture from the sterile site, such as in blood, as the basis for the definition of the cause of

pneumonia. Lastly, the common use of antimicrobials in the intensive care unit empirically are used for infections of other sites or organs.

[Slide.]

The next slide presents the implicated pathogens in nosocomial bacterial pneumonia. They are the gram-negative enteric bacilli, which are the predominant microorganisms, gram-positive cocci including Staphylococcus aureus, especially methicillin-resistant strains, and other gram-positive cocci, such as Strep pneumoniae, you have important isolates. Anaerobic bacteria account for a few cases, and lastly, other microorganisms including Legionella pneumophila and other species, as well as Haemophilus influenzae.

[Slide.]

The diagnosis of nosocomial bacterial pneumonia should be based on the clinical, radiographic, and microbiologic criteria which will be presented here.

First, let me talk about the proposed clinical inclusion criteria, fever or hypothermia, leukocytosis or leukopenia should be present. Please refer to the document for the definitions.

[Slide.]

Continuing on the inclusion criteria. At least two of the following signs and symptoms should be present: a new cough, new onset of purulent sputum or significant changes in the character of sputum or tracheal secretions are significant, or dyspnea, tachypnea, if any or all of these are progressive in nature.

[Slide.]

Continuing on the inclusion clinical criteria. Evidence of hypoxemia by pulse oximetry or by arterial blood gas determination, respiratory failure requiring mechanical ventilation, and in intubated patients requiring increased oxygenation.

[Slide.]

The chest radiograph taken within 48 hours by initiation of therapy should show a new or evolving infiltrate or infiltrates which is not related to another disease process, such as congestive heart failure, atelectasis, or ARDS.

There is a caveat to this. The state of the hydration of the patient should be considered at the time of the initial radiograph. Repeat films after hydration or diuresis are acceptable provided they are taken within the above time frame.

[Slide.]

Let's go to the microbiologic criteria. The Gram stain and culture of the sputum or respiratory tract secretions obtained by methods mentioned in the document, microscopic examination of the Gram stain specimen should show presence of microorganisms and less than 10 squamous epithelial cells and greater than 25 polymorphonuclear cells per low powered field for suitability of culture.

Antimicrobial susceptibility testing should be performed on pathogenic isolates. Alternate diagnostic tests may be used to establish infection, for example, pneumonia due to Legionella pneumophila and other species.

Isolation by culture is preferred, however, the use of such alternative tests should be discussed with the Division prior to initiation of this study.

[Slide.]

Continuing on. Two sets of blood cultures, aerobic and anaerobic from two different sites, should be obtained prior to initiation of the study drug in all patients. Blood cultures taken up to 48 hours prior to initiation of therapy are acceptable.

Antimicrobial testing should be performed on pathogens associated with respiratory tract infections.

[Slide.]

In cases where multiple pathogens are isolated in the sputum, the blood culture isolates should be utilized to corroborate with the sputum culture results.

[Slide.]

Because in the evaluation of nosocomial pneumonia there does not seem to be consensus in the literature on the criteria for interpretation of the culture results of the specimens obtained from mechanically ventilated patients, the proposed assessment plan for the culture data should be written down and presented to the reviewing division a priori.

[Slide.]

In pediatric populations, the clinical and radiographic criteria are the same as in adults, however, the definitions of fever and leukocytosis are different from those in the adults. The definitions are found in the new document for your reference.

Since there is difficulty in obtaining sputum in pediatric patients, then, blood cultures could be substituted.

[Slide.]

These are the proposed exclusion criteria.

Patients excluded in the indication of community-acquired pneumonia and patients excluded under general considerations, however, COPD patients are not excluded. Patients with sustained shock, patients with APACHE II score of less than 8 and greater than 25. Patients with known or suspected concomitant bacterial infection requiring additional systemic treatment.

[Slide.]

To continue on. Patients with chronic immunosuppressive therapy, patients with neutropenia, patients with epilepsy or seizure, patients with recent evidence of alcohol or drug abuse or dependence.

[Slide.]

On drug and drug dosing regimens, the proposed duration of the study drug and comparator drug may vary depending on the specific antimicrobial agent and respiratory pathogen isolated.

[Slide.]

Evaluation visits include pre-therapy, on-therapy, end-of-therapy, early post-therapy--they are both optional--and the test-of-cure visit.

[Slide.]

The pre-therapy visit, there should be

documentation of history including risk factors, physical examination, chest x-ray, laboratory tests including Gram stain, culture and susceptibility testing, blood cultures, baseline oxygen saturation by pulse oximetry or arterial blood gas.

The APACHE II score, if available, should also be included in the ICU patients to assess the severity of the illness.

[Slide.]

On-therapy visit. The daily assessments should be recorded in the case report form, and the laboratory assessments to be made during this visit should be tailored to the antimicrobial agent under study.

[Slide.]

Continuing on. There are general principles to be considered during this visit. Number one, a culture of respiratory tract secretions obtained by semi-invasive technique or techniques and susceptibility testing should be obtained at 72 hours after initiation of therapy in patients who are clinically failing.

[Slide.]

Blood cultures and susceptibility testing should be repeated at 72 hours if positive at entry or if patient

is clinically failing.

[Slide.]

The test-of-cure visit should be at least 7 to 14 days. I beg to correct. The one in the Blue Book is 7 to 21 days. This should be at least 7 to 14 days after completion of therapy. Repeat culture and susceptibility testing should be done in patients with continuing significant respiratory secretions to assess microbiologic response and to monitor the emergence of resistance.

[Slide.]

The clinical outcome is the primary efficacy variable for the indication of bacterial pneumonia. Dichotomous clinical responses include clinical cure and clinical failure. I would refer to the document for the respective definitions. All failures should be carried forward at the test-of-cure visits.

[Slide.]

The microbiologic outcomes include the following responses. Eradication or documented eradication, presumed eradication, persistence or documented persistence, and presumed persistence. Again, I would refer to the document for the respective definitions.

[Slide.]

Questions to the advisory committee members and Dr. Craig. How should we set the diagnostic criteria for ventilator-associated pneumonia, which is a revisit from the previous advisory committee in 1997? Should we screen bronchoalveolar lavage specimens in a similar manner as sputum (in terms of cytological screening) to determine the adequacy of specimen?

[Slide.]

I would like to express thanks to my following colleagues in helping out with the review of this guidance document: Dr. Renata Albrecht, Dr. Mercedes Albuerne, Dr. John Alexander, Dr. Sousan Altaie, Dr. Lillian Gavrilovich, Dr. Holli Hamilton, Dr. Mamodikoe Makhene, and Dr. Alex Rakowsky.

With that, I conclude my presentation. I would entertain comments and questions. Thank you.

DR. CRAIG: Any questions for clarification? Okay.

Committee Presentation

DR. CRAIG: I might comment that the criteria and the things for nosocomial pneumonia really reflect much of the discussion that we had at the March 1997 meeting. While I think at the time the committee realized that by requiring

fever and leukocytosis or hypothermia and leukopenia, that we would be knocking out some patients, such as the elderly, but we did think though that what we would be doing is we would be increasing the specificity that what we were dealing with was clearly nosocomial pneumonia.

So, I again continue to support that addition that was put in to the guidelines for nosocomial pneumonia requiring both fever and leukocytosis, because I think it does give us more specificity of what we are dealing with is pneumonia, because it can be other things that can cause changes on the x-ray, and what we don't want to do is be approving a lot of drugs for treatment of tracheal bronchitis and really what we are looking at is using the drugs for the treatment of nosocomial pneumonia.

We felt very much at that time, too, that for ventilation-associated pneumonia, that we also wanted to have that. We wanted to have fever and leukocytosis as being criteria, but when it came up to what do we do about interpreting cultures, how do we get those kind of cultures, my reading of the literature now is still a mix.

If you go to France, clearly, what they believe is that we need to do brushes and get down to the lower secretions and if you do your studies in France, you can

probably get such studies.

If you do your studies in the United States, it is going to be much harder to get that. Here, I think there is a little bit more now with pulmonologists in the United States to do BALs, bronchoalveolar lavage, so that a bronchoalveolar lavage tends to be more commonly used here, and again quantitation of the bacteria, ensuring that you have greater than 10^5 has been one of the techniques that has been used to try and correlate that.

What you would really like is studies that look at a whole variety of techniques and find out which one is the most sensitive. I am aware of an abstract that is going to be presented at ICAC this year that actually does that, and they actually found that quantitating the organism out of the sputum was actually about as good as doing more sophisticated techniques and trying to identify and correlate it with pneumonia.

Again, the question always comes up in those studies what is really your gold standard, and they were tending to use the brushed method as more the gold standard.

So, I still have a lot of difficulty in coming up with what I would use for criteria for ventilation pneumonia. I think clearly I would want I think quantity.

If it is truly causing infection, you are going to see the organism on the Gram stain, so it should be there in sufficient numbers, and whether that is sufficient enough, seeing a large number on the Gram stain, may be as good as we are going to be able to do in terms of quantitation, that there is more problems set with trying to do a quantitation in various laboratories where it is not necessarily standardized, that doing those kind of techniques may be more difficult and may not provide us any more information than what we get with looking at the numbers of the Gram stain.

So, I will be very interested to hear what Dr. Reller has to say about the last topic and the discussion that comes from that when we talk about the Gram stain.

The other question that was brought up at the end also refers to this in terms of BALs. I think when you put the scope down there, at least my experience with the BALs that I have seen, is that in infections, there is a relatively low frequency of finding epithelial cells. One finds sometimes bronchial epithelial cells, but not squamous ones.

So, I don't think you would have much problem in meeting those criteria if one wanted to apply it to a BAL,

because usually you don't find many of those cells present done in a correct method.

Other comments, questions?

Committee Discussion

DR. CRAIG: Carl, you have done enough things of this, you must have some comments.

DR. NORDEN: Our pulmonologists do BALs in the ICU in nosocomial pneumonia, and they tend to get purulent material out without huge numbers of epithelial cells. I agree with that. I don't think we will ever get protective brush the way the French do it in the United States. The French do think it is the only way to go, and that is the only study they will do for nosocomial pneumonia in general.

I am still not convinced also that simple, looking at the sputum, even in ventilated patients, or suctioning material may not be the way to go if you get large numbers of organisms, but I don't know, I truly don't know. I wrestled with this when I was in industry and I am wrestling with it still when we are dealing with patients in the ICU.

DR. CRAIG: It does provide some quantitation, if you can see it there on the Gram stain, you are usually talking about around 10^5 organisms in a sputum. Clearly, we find it frequently in our ICU in the patients we see, where

we see a rare organism around in the sputum or a few organisms, but it still cultures out moderate, sometimes even heavy growth out in the laboratory, so I am not sure that the information that we get from the laboratory tells us much, but, boy, when they get fever and they get sick, usually, we can see significant numbers of organisms on the Gram stain. So, we do find the Gram stain useful in this disease.

DR. SANTOS: Sandy Santos, Nexstar.

Another contribution from the French investigators is looking at the Gram stain of bronchoalveolar lavage and counting cells, phagocytes with intracellular organisms, and I wonder if you would comment on that.

I also wonder why, since I wasn't at the March meeting, why you were excluding patients who have seizures.

DR. CRAIG: Have seizures?

DR. SANTOS: One of the exclusion criteria listed in the document, and mentioned today, was the exclusion of patients with seizures or epilepsy.

DR. DAVIDSON: This would refer to patients who have recent seizure or epilepsy of high risk of aspiration. I think they should be excluded.

DR. CRAIG: I see. So, the reason it was, was

that the pneumonia may be aspiration pneumonia, still acquired in the hospital, probably still with nosocomial pneumonia, but usually since these are oftentimes a mixed aerobe and anaerobe, we oftentimes don't get the aerobic culture components, so I think really what we are looking at in most of the studies is the effect of drug in aerobic nosocomial pneumonia.

Am I right in that?

DR. SANTOS: I think that is correct, but given that scenario, in fact, you think that is a reasonable exclusion? I mean should we be including patients with potential aspiration pneumonia given their potential difference in pathophysiology and response?

DR. CRAIG: Yes, the problem that you have.

DR. SANTOS: Right, and the issue of the possibility of a chemical pneumonitis, as well, due to aspiration of gastric acid, do those represent a sufficiently different patient population that they shouldn't be included in the studies?

DR. NORDEN: I think the pathogenesis of most pneumonia, even nosocomial--

DR. CRAIG: Aspiration.

DR. NORDEN: And what happens we think in

nosocomial pneumonia is the patient is lying there, often with a ventilator, you have changed his or her flora with antibiotics, but then they aspirate, so I am not sure I would eliminate seizures, I wouldn't just eliminate patients with seizures, because there is so many reasons why they aspirate.

DR. CRAIG: But gastric acid, that's a different story. Those kind of aspirations from vomiting and everything bring in the issue of a chemical pneumonitis, which is a different story than somebody that essentially has a potential of aspirating oral organisms down to the lung, so while I would probably, as Carl said, not necessarily feel that I had to exclude patients that had seizures, but I would be very concerned about including aspiration essentially coming from the gut and a chemical pneumonitis in those patients, because it is hard to differentiate what it is and oftentimes what we are doing with antibiotics in most clinical situations is giving the drug prophylactically, so in case there are organisms that were tossed down there, we are preventing that from occurring than we are waiting until it actually turns into a bacterial pneumonia.

DR. NORDEN: The first part of your question, I

think the real problem that I have at least with techniques for culturing for aspiration is that everybody sort of has their own technique, and what they do, they may do very well, so the French do protective brush, Richard Mayhall believes in bronchoalveolar lavage with quantitation. Nobody has got as far as I know real comparisons. I mean you can't do too many procedures at the same time on a patient who is on a ventilator and has nosocomial pneumonia, and is fragile.

So, I don't know that there is any data that says what is the gold standard. I don't think we really know. So, I think if the technique seems to work in one person's hands, that is great, but it doesn't mean that it is going to work in everybody's hands either.

DR. CRAIG: I think that is one of the reasons why the committee felt that they needed to try and tighten up the clinical diagnosis by having the fever, the leukocytosis to try and make sure we were dealing clearly with a bacterial infection and then using whatever techniques we do have readily available in the United States to get the organism that one can use to try and do it.

Since here you have got clearly a lot of organisms that can be present in the nasopharynx that could

contaminate the sputum, that is why in this entity I think it is exceedingly important that the criteria be relatively tight for the kind of Gram stain that you are going accept. Otherwise, you clearly have the potential of getting organisms that were clearly not the actual cause of the pneumonia.

DR. ALTAIE: Dr. Craig, if we are suggesting that we should include aspiration pneumonia, would you think we should analyze those as a subset including anaerobic culture for the subset?

DR. CRAIG: The problem that you are going to have with aspiration pneumonia is they have aspirated a lot of contents down there. It is going to be hard to get a Gram stain at least for a while. It doesn't have a lot of epithelial cells. So, many of those patients would essentially fall out from some of those criteria.

DR. RELLER: I think what was attempted, and I don't know when these came in, I don't remember a specific discussion about excluding the patients with seizures, but I would be cautious in excluding patients, how this was phrased, because of the recognized pathophysiology of all these pneumonias is incorporating aspiration, so simply saying no aspiration pneumonia, but what I think the attempt

was is the gross obvious recognized recent large-scale inhalation of gastric contents, and to analyze those as a subset, trying to sort out the bacteriology with anaerobic cultures, I think is an exercise in absolute, complete futility.

What I would do is whatever language is necessary to either by history of seizures or recent seizure or gastric aspiration, to delineate that exclusion and not try to make sense of it after the fact, but to retain the basic entity that we all face every day, namely, those patients who are very sick, intubated, who are sick with pulmonary deterioration or pulmonary infiltrates for which we unfortunately don't have good validated cross-cultural, cross-country objective criteria.

But we can make some stabs at it that will be discussed later, to address one specific question about should we screen BALs in a manner like sputum in terms of cytologic screening, I am not aware of any published peer-reviewed criteria for doing that in contrast to the attempts of trying to spiff up the quality, the specificity of expectorated samples and endotracheal aspirates or aspirated samples where there have been published criteria.

Whether or not they are absolutely accepted and

how good they are is something we will discuss later, but at least they are out there for incorporation into clinical trials in contrast to grading BALs for this purpose, I know of no such criteria.

The use of BALs to diagnose bacterial pneumonia, at least in immunocompromised patients, there is a wonderful study from the Mayo Clinic on this issue, and they basically came up saying BALs are good for some things, but for making the diagnosis of bacterial pneumonia with the common pathogens, the Pseudomonas and E. Coli, very difficult, if not they would say impossible to separate out the real from the rubbish by culture of BAL.

DR. CRAIG: So, the point that you are bringing again is like we said before, there should be primarily a more clinical diagnosis, but that we are trying to at least be able to get organisms, techniques to get organisms that we can at least try and correlate a microbiologic response with the clinical response?

DR. RELLER: Yes. I think there is some analogies here, perhaps distant, but with a recognized entity of acute sepsis in a patient with a catheter in place in urinary tract infections. One of the difficulties with this entity, it is probable, and there have been some exceedingly--I mean

a great deal of effort has been put in to try to develop a gold standard, whether or not it was against which BALs and brushes and quantitative cultures obtained by brushing, et cetera, have been done including detailed microbiology of autopsy in patients who have done this, and probably why it is so difficult is that, in fact, it probably is a polymicrobial infection, and then you are trying to use ways to separate out the true polymicrobial infection that is in the lung parenchyma from the equal reality of polymicrobial colonization and inflammation that is present in every intubated patient, and the altered colonized mouth flora with gram-negative rods in people who are sick and have received antibiotics.

So, it is sort of like dealing in a morass, that the true reality is that it is polymicrobial in truth, but there are all of these confounders, and then how to get at that.

This is when the patient has a positive blood culture, their sort of salvation, in that there you are pretty reasonably certain that if someone has a positive blood culture with a putative pathogen with an infiltrate, and they have got nosocomial pneumonia, that the two may be linked, but in the absence of that, it becomes exceedingly

difficult, so all that one has are ways to try to at least avoid the most egregious discrepancies, and that is where attempts at assessing the sputum may have some utility, but it is not a perfect solution. We don't have a solution if we are honest.

DR. CRAIG: Yes.

DR. HAMMOND: Janice Hammond from Glaxo Wellcome.

I have got three comments. Firstly, are the alcoholics and the drug-dependent patients being omitted for the same concern of aspiration or was it because they were immunocompromised, because you might want to reconsider that one, too.

Secondly, the APACHE score, my concern with the APACHE score is that it is usually defined as the worst physiological parameters in the first 24 hours following admission. You might be wanting to follow acute physiology scores, but it only takes 24 hours to obtain those calculations that you are suggesting there.

My third question would be how you are going to handle patients who have been on prior antibiotic therapy.

DR. DAVIDSON: To address the first question was excluding patients with recent evidence of alcohol and drug, again, the issue of aspiration and also an issue of

immunosuppressed patients, there is the possibility.

The other issue of the APACHE score, well, as soon as patients are admitted in the intensive care unit, where the APACHE score is available, then, we would like to have those in the case report forms included.

DR. HAMMOND: Certainly, but if the patient is already in the ICU and then you are not going to get an APACHE score. You would probably want to amend that to have acute physiology score.

DR. DAVIDSON: Good point.

DR. CRAIG: Did everyone understand that? Could you clarify that?

DR. HAMMOND: The APACHE II score is by definition a score of the severe derangement of physiological parameters on admission to the ICU, and a lot of patients who develop nosocomial pneumonia will already be in the ICU, so that by definition, you can't calculate an APACHE II score on these patients.

You can certainly calculate the acute physiological, the SAP score, which is the physiological derangement parameters, but the APACHE II score also incorporates the chronic disease severity and underlying illnesses, which would not be appropriate.

DR. CRAIG: Again, many of these patients are not the ones that are already in intensive care, the ventilated patients would be, and that is a problem, you are right, with the criteria for ventilation pneumonia is you wouldn't be able to do it.

DR. HENRY: One question which really is probably pretty minor, it is just a clarification. The inclusion criteria now include leukopenia, but exclusion is neutropenia, and so what is your cutoff going to be?

DR. CRAIG: Well, neutropenia, what is your cutoff?

DR. RELLER: Tomorrow, we are discussing febrile neutropenia, and there the figure is 500. I think this is just recognizing that they have an exhaustion phenomenon, someone who has a white count who is really sicker than stink, and has got a white count of 4,000, but what you want to exclude is if they are less than 500. At least it would be nice to have it consistent with what we are discussing tomorrow.

DR. HAMMOND: My third point was the prior antibiotic use, which I think makes evaluation almost impossible. If the patient is already on antibiotics, how are you going to use your microbiological cutoff criteria

for obtaining a diagnosis, how are you going to evaluate these patients if they are already on an antibiotic?

DR. CRAIG: I think if it is relatively recent, what you have to have is an organism that is resistant to the drug that you are going to be looking at. It is the same criteria that has been used before.

Unless it has been a period of time, I mean the ideal thing for trying to get the approval for nosocomial pneumonia are people that are out on the wards and, you know, places like this, where they haven't been on an antibiotic, they come down with nosocomial pneumonia, and you can enter them in the study. Those would be the ideal patients for registration.

The more you start moving more to ventilation-induced pneumonia, you start coming up with more other causes that can produce the radiologic changes, you have got the patients on more antibiotics for other indications besides, not necessarily pneumonia, and it makes it a much more difficult group of patients.

They are out there, and there is plenty of them, and so they are easy to get to, but it makes it much more difficult to use those kind of patients for approval for this indication, at least in my mind it does.

DR. RELLER: I was going to address this also in the sputum Gram stain discussion, but Dr. Hammond raises a very important point. Many of these patients who are in the intensive care unit, who are intubated, the specimens that we get for culture, in fact, don't show organisms and grow out only when there are no organisms seen on Gram stain smear, grow out no predominant organism, in fact, either nothing or sparse flora.

They are sick, they have got pulmonary infiltrates, they are sick, and they are suspected of having an infectious etiology, but exclusion of those patients somehow I think is reasonable if one has any intention of making any objective correlation between a specific antimicrobial agent and a microbiological and clinical response.

I mean it is not saying that these people don't have infection, but how you are ever going to objectively assess response to therapy, I think becomes almost impossible in these patients who have been in the intensive care unit receiving antibiotics perhaps even repeatedly.

DR. CRAIG: So, I think the ones I can remember that, you know, turned out nice are the ones that haven't been on any antibiotics, are there for a period of time,

then, all of a sudden their Gram stain turns positive, they get fever, they get new infiltrate, and it is a lot clearer, but the ones that have been on antibiotics are exceedingly difficult.

DR. SANTOS: Sandy Santos. I would just point out an interesting conundrum in the criteria for ventilator-associated pneumonia. The ventilator-associated pneumonia criteria says that the infiltrate cannot be accounted for by another entity such as ARDS, but when you go to look at the guidelines for the evaluation of drugs in ARDS, it says ARDS is defined as an infiltrate that cannot be accounted for by a nosocomial pneumonia.

[Laughter.]

DR. CRAIG: Great. Does anyone else want to add another suggestions?

DR. RELLER: So, there is a consensus, Bill, in response to Dr. Hammond's query, that some exclusion criteria for nosocomial pneumonia would be appropriate having to do with prior therapy that would so cloud the issues of evaluation as to make it impossible?

DR. NORDEN: I am sorry. I missed part of this discussion. I don't know that that is always true. I think, first of all, it is almost impossible, it is very

rare to find patients now who aren't on antibiotics who get nosocomial pneumonia. I mean most of the people in our ICU, which is where you see a lot of it, obviously, are on antibiotics.

What strikes me is that many of them or at least some of them, they are on antibiotics, they are either slowly improving, and then they deteriorate, and it is often fairly quick - high fever spike, their respirations increase, and, you know, you look at a Gram stain, at least we do, and you see what you would predict. If they were on primarily gram-positive coverage, they are teeming with gram-negatives, and you switch them to gram-negative coverage, and some of them actually do improve.

I would hate to make a blanket exclusion criteria of prior antibiotic therapy.

DR. RELLER: Great, Carl. What you are saying is that the exclusion would not be absolute if one can demonstrate an organism that is present in that Gram stain sputum that would be corroborated with culture, you may even have a positive blood culture with the organism, so that the emphasis then becomes on the antibiotics are not an exclusion if what we are really talking about is like a superinfection that can be objectively demonstrated, but if

one doesn't have that objective demonstration of a putative pathogen with some reasonable criteria for tightness of the microbiology, then, you are floundering in the dark and consequently, would become unevaluable.

DR. NORDEN: I am comfortable with that scenario, yes.

DR. CHIKAMI: And your comment also spoke to clear clinical criteria for deterioration that is well documented, so that defining either a worsening of the condition or new symptoms that are well documented and compatible with development of, or worsening of, pneumonia in addition to the microbiologic criteria that Dr. Reller commented on.

DR. NORDEN: That is absolutely correct, and you certainly can't do that with every patient. I don't know how many you can do it with, but again I think if we made a blanket exclusion of prior antibiotic therapy or concomitant antibiotic therapy at the time you wanted to enroll the patient, you would have very few patients to ever enroll in a nosocomial pneumonia trial.

DR. CRAIG: My experience, too, and I don't know whether you would second this, Carl, is that frequently when those changes occur, fever and leukocytosis or at least an increase in the white count are frequently observed.

DR. NORDEN: Yes, yes, that is correct.

DR. RELLER: I would like to ask and also for the committee, the blood cultures repeated at 72 hours if positive at entry or if patient is clinically failing, I can see if clinically failing, but why have blood cultures repeated at 72 hours, at a fixed point, repeated at all in someone who is responding to therapy when they were previously positive? That, I don't understand.

DR. CRAIG: My feeling has been that it has always been the FDA's requirement if you had some positive ones, you eventually had to have some negative ones, and if you don't need that, and I agree that it doesn't make much rationale in somebody that is doing perfectly fine and responding to have those, but clearly in patients that are failing, then, I think it is helpful.

DR. RELLER: For some things, there are clear microbiological endpoints that need to be reproduced, but in a way it is like--I realize the blood is easier to get than the CSF--but in terms of consonant with clinical practice, you know, is there general recognition of the importance of documenting that the organism went away, and blood, when it is only in the blood because you haven't contained the primary infection which you are responding to therapy, in

contrast to someone who is failing, I can see, but in other words, to have the repetition of cultures be based on some delineated clinical criteria rather than being put in there as a test-of-cure, which I mean they are being drawn on antibiotic therapy, and I think that they are not interpretable.

DR. CRAIG: The only thing I know is in Staph bacteremia, but not necessarily in Staph pneumonia, where the speed at which the organisms disappear or persist can have some prognostic data and some impact on duration of therapy, but not for pneumonia. I know of nothing that would point for that for pneumonia.

Most of those times, I think what you are doing is you are going to get negative cultures and that is what you see.

DR. CHIKAMI: Right. I agree. I think that will clarify then that document, but I think clearly if there is a clinical indication the patient is failing, it would be reasonable on the basis of clinical practice to repeat the culture, but otherwise if the patient is doing well, there is not a requirement to repeat the blood cultures.

DR. CRAIG: Anything else?

Let's take the last item then which is Gram stain,

which will be presented by Dr. Sousan Altaie.

Sputum Gram Stain

FDA Presentation

DR. ALTAIE: Good afternoon again. It is good to have this topic for the last talk because it keeps people waiting and not leaving the auditorium.

[Slide.]

I am going to state what the current situation is in our pneumonias. Gram stain is currently part of inclusion criteria for the lower respiratory tract infections. That criteria is less than 10 epithelials and greater than 25 WBCs per low power field, and that is 100 X.

[Slide.]

I would like to discuss the following issues in regards to that. Why, first of all, do we screen this lower respiratory tract? I would like to set the record straight for that. And why do we use it that way?

What are Gram stain criteria for acceptability of culture results? Should the Gram stain be part of the inclusion criteria. How should the Gram stain in an overall picture of this indication be used?

[Slide.]

For the first issue, why do we screen?

[Slide.]

The upper respiratory tract to the level of larynx is the major source of contamination for most specimens, including expectorated sputum, nasopharyngeal aspirates, and bronchoscopy aspirates such as BAL. I do believe bronchoalveolar lavage is a contaminated specimen and it should be screened, as well as endotracheal aspirates as we see down the road.

[Slide.]

Gram stain smears should be prepared for all sputum submitted for bacterial cultures to determine the extent of contamination with saliva--referring to Dr. Reller's swishing the sputum in your mouth before put it in the cup--and that is the main reason for it, to determine how much it is contaminated before you put it on the culture to be expecting that the culture would give you a readable culture.

[Slide.]

Now, the background to this, I don't know how far back it went, but with me, prior to 1971, the laboratories use to culture anything that walked out through the doors, and it was in a cup. So, reports of "nonvalue" of the sputum cultures flooded the literature.

[Slide.]

This slide shows my favorite one by Liz Barret-Conner, that in '71, she said routine sputum cultures for the diagnosis of acute bacterial pneumonia may be a sacred cow. She was doing a study on Pneumococcus pneumonia, and her cultures were not productive about 40 percent of the times.

[Slide.]

In the clinical laboratories, there was a multiple effort and attempts to try to improve the quality of the sputum cultures. Several techniques were played with. Washing was one of the techniques where they cleaned up the sputum and picked up the purulent portion, and cultured that. That is a technique to got a hold in Europe, but never got a hold in the clinical labs in the U.S.

Quantitation was another method that was attacked, but with the problems associated with quantitation and the fact that the laboratories really did not have a picture of the clinical situation, we really could not set a break point for quantitation of these sputum cultures.

So, microscopic screening tended to get a hold in these laboratories in the U.S., and that became a practice, trying to determine contamination by the amount of

contamination by the oropharynx flora.

[Slide.]

What are these criteria? There are several criteria floating around, different laboratories use different criteria, and each one of them came from a background, and I would like to go through those backgrounds and explain how they came about.

[Slide.]

The first one is one of the classical studies was done by Ray Bartlett in Hartford in 1974. He looked at specimens as they walked in the laboratory without paying attention to the clinical picture, and put up what is called quality score, composite quality score, that takes into consideration the number of squamous epithelial cells and gives them a negative score. These are the bad guys. Then, you have the WBCs, and these are the good guys and you get a positive score for them.

So, you come up with a composite score in this rectangle here, and he said the ones that have a score of 1 or greater within that stepladder separation area, are the ones you need to culture, and those are the ones that have cultures that are interpretable.

If you pay attention to this, you will see the

productive cultures are the ones with less than 10 epithelial cells for the majority of the time regardless of the number of the WBCs.

[Slide.]

Pat Murray did a study in Mayo Clinic in '75, and he separated the groups 1 to 5 based on the number of epithelial cells and WBCs. This was the samples he collected in one month, and then he had transtracheal aspirate specimens in his lab that were collected in the past 12 months, in the same time period of the same year.

He had 47 of those samples, and he looked at what grew out of these cultures. He looked at all organism points out of those specimens, and he came up with an average of 2.4 per specimen, and the other groups had different numbers, and the only time that the number of organisms got close to what was in transtracheal aspirate was when the number of epithelials dropped to less than 10, not regards to 25 WBCs.

He makes the statement that said number of WBCs really bear no consequences of the outcome of the cultures.

[Slide.]

Geckler in '77, and his coworkers, also did a study. They took 96 patients with a clinical diagnosis of

pneumonia, and they did transtracheal aspirate in addition to collecting sputum, side by side.

They called the Strep pneumo, Haemophilus influenzae, Neisseria meningitidis, Group A Strep, and Staph aureus, intake rods as pathogens, and they only cultured specimens that they had less than 25 epithelial cells, and did not pay attention to number of the WBCs.

[Slide.]

What grew out of these cultures is the mean number of pathogens, as I defined them, not all the organisms, but just the pathogens, was less than 1. That is because some of the samples did not grow any pathogens, so you have a smaller number than 1.

So, this is the group that didn't make sense to culture, and those are the ones that had greater than 25 epithelial cells, but any number of WBCs, and he states that we could culture these groups, and he recommends this is the best group to culture, despite the fact, because these numbers are really low.

So, this is where the less than 25 epithelial cells started floating in the literature and laboratories started using it without regards to the WBC count.

[Slide.]

They are looking at endotracheal aspirates, they are screening endotracheal aspirates. As I said, I think they are contaminated, they are aspirate specimens, they need to be screened.

In their laboratory, when they do the same comparison, this is number of organisms growing out of the culture, every time that they had less than 10 epithelial cells, the number went down in all the groups of WBCs, so otherwise it didn't matter how many WBCs you had as long as you had less than 10 epithelial cells, you had low number of organisms growing.

[Slide.]

They take the concept one step ahead and they say we not just want to screen for epithelial cells, we just want to also look at the presence of organisms on those slides and determine whether presence or absence of organisms do play a role in determining an etiology for the pneumonia.

As you see most of these met the criteria, but did not have organisms, ended up to be either sterile, 88 percent of them ended up to be either sterile or having rare amount or various degrees of normal flora. We are losing a little bit of gram-negatives here and here, around 5 percent

would contain pure gram-negative isolates in lower counts, and at the expense of losing these patients, they decided that they are going to screen for presence of organisms and less than 10 epithelials. In that way, they were sure that they are going to give the physicians a productive culture that points to the etiology of pneumonia.

[Slide.]

So, I think I presented enough information to state that I don't believe the presence of WBCs on the Gram stain really bears any consequences as far as what is going to grow on this slide, and I like to hang onto the less than 10 epithelial cells and set that as a criteria.

[Slide.]

Now, how should this sputum--this is the next issue that I was going to address--how should sputum Gram stain results be used?

[Slide.]

This is a study done by Gleckman, et al., in 1988. They did a prospective study for four and a half years to determine the ability of sputum Gram stain to predict the cause of community-acquired pneumonia.

They used blood culture isolates rather than the sputum culture as the gold standard for the reference of the

etiology. They ended up with 59 specimens, and they entered them based on the WBC and epithelial cells.

To refer to Dr. Craig's statement that if you see the organisms on the Gram stain, they really have the disease and that the predominant organism actually changes 1 per oil field equals to 10^5 organisms. They were counting greater than 10 organisms per oil field as a significant bacterial count, and so when they interpreted their Gram stains, they were looking for this number before they called an organism.

Despite this, that the sputums were screened and they were then cultured, 12 of the specimens did not produce a helpful result in determining the etiology of the pneumonia just for certain reasons, they had multiple organisms or pathogens, and so on, and so forth, which I don't need to go into the detail for.

In the remaining 47 percent, the Gram stain did predict in the remaining 47 patients, the Gram stain did predict the blood culture isolate with a sensitivity of 85.1 percent.

[Slide.]

Now, they conclude that if a clinician had been guided by the valid Gram-stained sputum, and offered a

monotherapy, the initial therapy would have been ideal for 40 patients and suitable for four, and not suitable for three patients.

That gives you an overall 94 percent of the time, giving appropriate monotherapy based solely on the Gram stain.

[Slide.]

I like to show this. This is how the organisms broke down and where they failed was where the Haemophilus influenza was the causative agent, and the Gram stain just determined that is it is a gram-positive infection versus a gram-negative infection, and so this is two of the patients that failed.

Down here again, another Haemophilus influenza failed being presented on the Gram stein as an interior gram negative. So, Haemophilus is hard to see on the Gram stains, and that is where you fail with the Gram stain.

[Slide.]

So, I think Gram stain results should be used to determine the adequacy of the sputum specimen, to produce an interpretable culture that may lead to the etiology if the lower respiratory tract infection.

DR. ALTAIE: Should Gram stain be part of the

inclusion criteria? I think this is very important to note that we should not overlook that the pneumonia is a clinical diagnosis. Microbiological procedures are only of value for attempting to establish an etiology for the pneumonia.

To confirm the diagnosis of pneumonia, not to make the diagnosis of pneumonia.

The Pneumonia Diagnostic is based on clinical findings which are in the X-rat,

[Slide.]

Culture results should be interpreted by correlating clinical observations with the results of direct examination, cytology screens, and quantitative or semiquantitative culture, as well as the pathogenic potential of the organisms that are recovered in culture.

[Slide.]

With that, I would like to thank again my colleagues in the group and for their continuous support.

[Slide.]

I would like to leave you with the thought of the day, and I am open to questions.

DR. CRAIG: Any comments, questions? Dr. Norden.

DR. NORDEN: First of all, I want to thank you for presenting data which I have never seen before on the

relationship of Gram stain, the white cells, the epithelial cells. I would just comment if you go back and look at Bartlett's data, that you could look at it in another way and say that at anytime you have more than 25 white cells, you have a useful specimen unless it has more than 25 epithelial cells, too.

So, I think you don't want to totally discount the white cell component. I will save my other comments until later.

Committee Presentation

DR. RELLER: There is I think a fine review of the microbiology in the interplay that Dr. Altaie has I think appropriately pointed out between the clinical and microbiological issues in a review article in Clinical Microbiology Updates in Clinical Infectious Diseases early this year, written by Karen Carol and Larry Reimer.

They, as well as the infectious diseases group from the Mayo Clinic, have repeatedly stated, and I think appropriately, that where one gets into controversy is not recognizing that the microbiology evaluation is not a test for the presence of pneumonia.

One starts out with pneumonia and then microbiology can help assess etiology if criteria are in

place for providing a good sputum. This is a topic that has generated an enormous amount of controversy because of not having the proper sequence of events.

For example, when we look at specimens that have been rejected of the sputum specimens, fewer than 5 percent of those patients have a radiograph consonant with pneumonia, so that one has to start out, and this also in part explains how one might come up with discrepancies between the American Thoracic Society guidelines and the recently published IDAS guidelines.

One, chucking sputum microbiology all together, and the other emphasizing it very much. There are multiple screening criteria. The one we used and what led to the Morris study presented with ETS specimens, and the same has been published for pediatrics for Anita Zaidi, with the same conclusions. In endotracheal aspirates from pediatric patients, and the utility of Gram stain in screening and correlating with our culture results and coming to an etiology, there are many, but the one we use, and what led to the Morris study is based on the most commonly used one, namely, that from the Mayo Clinic.

There, the primacy is on squamous epithelial cells as the most simple, useful assessing quality of specimen. I

agree totally with Carl and usually it is not an issue because if the patient is not granulocytopenic and you have got a good quality specimen, and most importantly, they had pneumonia before you sent the specimen based on a hydrated patient with an infiltrate on chest radiograph. It's a non-issue.

We happen to emphasize the squamous epithelial cells because we find it very useful in immunocompromised patients who may be granulocytopenic, and not have the polys present, but for the purposes of this document, where the granulocytopenic patients are being excluded, probably less than 500, then, I see no reason for putting the emphasis on the clinical entity of a purulent sputum in a patient with a positive chest radiograph of going ahead and retaining, that you would like to see that assessment also, namely, the presence of polys because it reinforces that these patients have the purulent sputum, but for an acceptable specimen and for an evaluable patient, I think the best, not the only, but the best, most used and best validated, because it has been validated in endotracheal suction specimens from the nosocomial pneumonias, as well as the expectorated specimens in the patients with community-acquired pneumonia, that it makes it easier to keep track of things, so I completely

agree with what is presented here.

Just as a final comment, a culture without a Gram stain is dicey proposition. In fact, I would go further and say it's worthless, and a culture without pneumonia can't provide a diagnosis for what doesn't exist, or put another way, I mean this is sort of like the Drucker comment, about if it's not worth doing, it's not worth doing well, so if the patient doesn't have pneumonia, it's not worth culturing, but if it's worth culturing, it's worth doing it well.

I think well is what gives one a reasonable shot at an objective assessment of a potential etiology, and that includes an obligatory requirement for all of these pneumonias to have an assessed quality of sputum on which to make a reasonable attempt to make the etiologic correlations.

And the quantity, coming back to an earlier comment of Bill's, I think is important. Not shown here, but a part of that Morris publication for endotracheal aspirates that were largely nosocomial pneumonias, occasionally, some of them were patients who were so sick that they were intubated and the first specimen obtained in the community-acquired pneumonia in the intensive care unit

was an endotracheal aspirate, and it also applies to the pediatric patient is clearly, and in that paper is the correlation of culture results with presence of organisms on the Gram stain smear.

In our laboratory we don't culture endotracheal aspirates that don't show organisms, I mean we don't culture them, period, because it just leads to confusion, but the best correlation was with 3-4+, a large number of organisms, just the scenario that Dr. Norden pointed out earlier with the superinfections, that the endotracheal aspirate is loaded, for example, with gram-negative rods, and those that are 3 or 4+ on the Gram stain, you grow out an Enterobacteriaceae, sometimes two, but they are there in large numbers, and that is where you have got a reasonable shot at correlation.

So, I think the quantitation is important because it is going to give you the most likely correlate with the culture having to do with delineation of possible etiology. It is not perfect. There may be better things, but it is the best way we have at the moment of trying to bring objectivity to the etiologic assessment in patients who clearly by clinical and radiographic criteria have the entity in the first place.

Committee Discussion

DR. CRAIG: Dr. Norden.

DR. NORDEN: As usual, Barth, you are clear and eloquent, and I really agree with essentially everything you said. I have a couple of concerns. One is the adequacy of interpretation and reading of Gram stains in many centers. We are doing a study with the CDC, we have a large grant to look at pneumococcal infections in the community, and there are about 25 hospitals involved. The Gram stains are saved from the hospital with their interpretation and then read by one of our microbiologists who does nothing else but read those for us, and there is at least a 50 percent discrepancy, so I think that we may need to have some kind of standardization or even central interpretation of Gram stains in clinical trials, because I don't trust, frankly, all of the material that we are getting.

The other comment is just the question about still whether it should be an inclusion criteria Gram stain, and I agree with you completely that pneumonia is a clinical diagnosis and if you don't think the patient has pneumonia, you shouldn't send the sputum to the lab, but in some clinical trials at least I think we are looking primarily for bacterial pneumonias, and the x-ray isn't specific, and

even the clinical picture may not be specific, and so will we be including patients with influenza, Legionella, maybe we should be, but with viral pneumonias, and it would seem to me that a purulent sputum in which you see organisms enhance enrollment of patients that you want to study.

DR. RELLER: I agree with you completely. I mean I think what is being said is that to be included in a trial of an agent directed against a bacterial etiology, that one needs pneumonia in the first place, and a sputum specimen that passes muster, and one needs both of those things absolutely, both of those, to end up with a patient who can be evaluated at the end of the day.

Your earlier comment about central validation, I think is a good one. Unfortunately, and this is an issue that I hope gets greater attention in the infectious disease and medical community at large, is the provision of quality microbiology diagnostic services to support the diagnostic efforts of clinicians in this nation is a resource that is at risk.

DR. CRAIG: I agree, and I think what the industry has been doing a lot, too, is moving more to central laboratories where a lot of the things are essentially removed from the local laboratory, so that they are not

really being supported.

DR. RELLER: This may be a safety net for clinical studies, but it does not bode well for patients who then subsequently are treated with these agents by clinicians in this nation.

DR. CRAIG: Very true.

Are there any other comments or disagreements or anything with what has been said? Do you have any more questions from the agency?

DR. CHIKAMI: No, not at this time.

DR. CRAIG: So, another day is done. Tomorrow we will start again bright and early at 8:00. There is nothing for the open public hearing tomorrow afternoon at 1:00 to 1:30, so we will just continue until we are done and when we are done, you can have lunch, so there won't be a break tomorrow. I have been told we have one speaker for tomorrow, but we will move that person up. We will still go on through and get done.

[Whereupon, at 5:20 p.m., the proceedings were recessed, to be resumed at 8:00 a.m., Friday, July 31, 1998.]

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